Differential Diagnosis of Internal Diseases

A.V. Vinogradov

Volume 2

Mir Publishers Moscow

Differential Diagnosis of Internal Diseases

A.V. Vinogradov

Volume 2

Differential Diagnosis of Internal Diseases

А. В. Виноградов

Дифференциальный диагноз внутренних болезней

Том 2

Издательство «Медицина» Москва

Differential Diagnosis of Internal Diseases

A.V. Vinogradov

Translated from
the Russian by
Ludmila Aksenova, M. D.,
and Arthur Aksenov

Volume 2

Moscow Mir Publishers

First published 1982
Revised from the 1980 Russian edition

На английском языке

© Издательство «Медицина», 1980
© English translation, Mir Publishers, 1982

Contents

Chapter XI. Gastro-intestinal Haemorrhage 345

Aetiology of Gastro-intestinal Haemorrhages 347
Diseases of the Stomach and Duodenum 348
Diseases of the Oesophagus 353
Portal Hypertension 355
Diseases of the Intestine 358
Other Diseases 363

Chapter XII. Goitre with Thyrotoxicosis 367

Diffuse, Nodular and Mixed Goitre 367
Tumours of the Thyroid Gland and Other Organs 369
Thyrotoxicosis Caused by Iodine or Thyroid Preparations 371
Thyroiditis 372

Chapter XIII. Haemoptysis and Pulmonary Haemorrhage 374

Haemorrhage from the Upper Respiratory Tract 377
Haemorrhage from the Trachea and Bronchi 377
Diseases of the Lungs 379
Diseases of the Cardiovascular System 382

Chapter XIV. Heart Failure 384

Right-ventricular Failure 384
Chronic Cor Pulmonale 396
Biventricular Heart Failure 399
Diseases of the Heart Muscle 399
Myocarditis 400
Congestive Cardiomyopathy 403
Rare Diseases 407
Amyloidosis of the Heart 411
Left-ventricular Failure 413
Mitral Stenosis 413
Atrial Septal Defect 425
Myxoma of the Left Atrium 426
Mitral Insufficiency 430
Aortic Stenosis 439
Aortic Insufficiency 448

Chapter XV. Heart Murmurs 460

Innocent Murmurs 461
Continuous Murmurs 464
Systolic Murmur 468
Diastolic Murmur 487

Chapter XVI. Hepatomegaly and Splenomegaly 496

Acute Anicteric Hepatitis 497
Chronic Hepatitis 497
Cirrhosis of the Liver 502
Cysts and Tumours of the Liver 511
Diseases of the Hepatic Vessels 520
Diseases of the Blood and Haematopoietic Organs 527

Chapter XVII. Jaundice 535

Jaundice with Unconjugated Bilirubin 536
Non-hepatogenic (Haemolytic) Jaundice 536
Hepatogenic Jaundice with Unconjugated Bilirubin 540
Jaundice with Conjugated Bilirubin 542
Hepatogenic Jaundice with Conjugated Bilirubin 543
Extrahepatogenic (Obstructive) Jaundice 555

Chapter XVIII. Oedema (written jointly with M. A. Vinogradova) 564

Oedema Occurring Mainly under the Effect of Local Factors 566
Lymphatic Oedema 567
Premenstrual Syndrome and Oedema in Pregnancy 568
Nephrotic Syndrome 569
Glomerulonephritis 572
Diffuse Diseases of the Connective Tissue 574
Systemic Vasculitis 576
Infectious Diseases 579
Amyloidosis 580
Secondary Amyloidosis 580
Familial Amyloidosis 583
Malignant Tumours 584
Diabetic Nephropathy 586
Other Causes 587
Enteropathy with Excessive Protein Loss 589
Intestinal Lymphangiectasis 591
Sprue Syndrome 594
Tumours of the Small Intestine 598
Whipple's Disease 600

Chapter XIX. Paroxysmal Dyspnoea 605

Diseases of the Lungs 605
Diseases of the Cardiovascular System 608
Other Diseases 616

Chapter XX. Peripheral Vasospasm 619

Raynaud's Disease 619
Raynaud's Syndrome 620
Livedo Reticularis 626
Acrocyanosis 626

Chapter XXI. Pleurisy 629

Identification of the Pleural Effusion Syndrome 629
Causes of Pleural Effusion 632

Chapter XXII. Pneumonia 643

Acute Pneumonia 643
Bacterial (Gram-positive) Pneumonia 644
Bacterial (Gram-negative) Pneumonia 651
Virus and Mycoplasmal Pneumonias 656
Chlamydian and Rickettsial Pneumonias 661
Allergic Pneumonias 665
Pneumonias Caused by Certain Physical and Chemical Factors 669
Unresolved Pneumonia 674
Lobar and Segmental Pneumonias 680
Lobular Pneumonia 688
Diffuse Miliary Pneumonias 697
Prehilar Pneumonia 702

Chapter XXIII. Polycythaemia 708

Congenital Polycythaemia 713
Hypoxic Polycythaemia 714
Relative Polycythaemia 716

Chapter XXIV. Polyuria and Polydipsia 717

Diabetes Mellitus 718
Diabetes Insipidus 719
Polyuria in Disorders of Other Tubular Functions 722
Fanconi's Syndrome (Adult Type) 723
Tubular Acidosis 724

Hyperparathyroidism and Hypercalciaemia of Other Origin 725
Conn's Syndrome and Hypokaliaemia of Other Origin 727
Other Diseases of the Kidneys 729
Involuntary Polydipsia 730

Chapter XXV. Purpura 734

Thrombocytopenic Purpura 736
Werlhof's Disease 738
Non-thrombocytopenic Purpura 741

Chapter XXVI. Transient Loss of Consciousness 749

Vasodepressor Syncope 751
Postural Hypotension 752
Acute Diminution of the Circulation Volume 757
Pleural Shock 759
Mechanical Obstruction of the Blood Flow 759
Primary Diseases of the Nervous System 761
Increased Carotid Sinus Activity 767
The Aortic Arch Syndrome 770
Heart Arrest and Arrhythmias 772
Pulmonary Hypertension 774
Metabolic Disorders and Other Conditions 776
Bibliography 783
Subject Index 788

Chapter XI

Gastro-intestinal Haemorrhage

Protracted but small-volume haemorrhages from the gastro-intestinal tract become the focus of attention only after they lead to the development of anaemia. Acute massive haemorrhages are often complicated by the clinical picture of haemorrhagic shock. In such cases the physician's diagnostic work in identifying the cause of bleeding is conducted simultaneously with therapeutic measures for the control of shock and arrest of bleeding. The volume of diagnostic investigations varies from one patient to the other and is determined by the severity of the condition. In each case it is necessary to determine the amount of blood loss and the rate, cause and localization of the bleeding. The problems arising meanwhile may be solved by the joint efforts of the internist, surgeon and radiologist who draw up a plan of emergency therapeutic measures even to the point of operative intervention.

Most gastro-intestinal haemorrhages are intermediate in character between these two extremes. Their numerous causes are listed in Supplement XI-1. Massive haemorrhages are usually encountered in acute gastric erosions, gastric and intestinal ulcers, portal hypertension, tumours of the gastro-intestinal tract, and haemorrhoids. Other causes are rarely encountered in the internist's practice.

The clinical picture of massive haemorrhage is quite monotonous. A patient who is sound in health suddenly experiences weakness, dizziness and tinnitus, his skin turns pale and becomes covered with cold sticky sweat. The pulse becomes rapid and thread-like, and respiration becomes shallow. The systolic arterial pressure falls below 80 mm Hg for some time. The patient may be so weak that he can hardly reply to questions. In milder cases the patient attempts to rise, but often faints because of diffuse ischaemia of the brain. The cause of this unusual weakness and fainting becomes obvious only when bloody vomiting and a tarry stool appear.

In most cases bloody vomiting occurs soon after the beginning of profuse haemorrhage. The colour of the vomit depends on the rate of bleeding. In moderate haemorrhage, the haemoglobin released from the disintegrated red cells has time to react with hydrochloric acid. The hydrochloric haematin formed as a result lends the vomit the typical appearance of coffee dregs. A dark cherry colour of the vomit is evidence of more rapid bleeding. A crimson vomit is encountered either in bleeding from the oesophagus or in cases of pro-

fuse and rapid bleeding from the stomach when the blood is discharged with no time to react with hydrochloric acid. A bloody vomit may also be observed in bleeding from the duodenum on condition that it occurs when the pyloric canal is opened.

The intestinal motor function is stimulated the more sharply, the more massive the bleeding. It was established in experiments on volunteers that a tarry stool is passed after no less than 100 ml of citrated blood is taken per os. After one or two litres of blood is taken, the stool remains tarry for three to five days, while the test for occult blood in the faeces is positive for two or three weeks. It follows from these data that a tarry stool does not always indicate massive bleeding and that melaena of many days' duration may also be observed in a single massive bleeding and that positive test for occult blood in the faeces does not provide evidence that the bleeding is still continuing.

Melaena without preceding bloody vomiting is mostly encountered when the source of the bleeding is localized distal to the pyloric part of the stomach, though infrequently it also occurs in haemorrhages from oesophageal varicose veins and from a gastric ulcer. Most authors claim that the colour of the faeces is determined by the localization of the bleeding and the time the blood stays in the intestine. Bright red blood appears in the stool 4 to 17 hours after oral administration of 1 litre of citrated blood.

A tarry stool is observed as a rule when the source of the bleeding is proximal to the ileocaecal valve, but Schiff (1970) reports that he also encountered tarry stools in bleeding from the caecum. The discharge of unaltered blood is usually observed in bleeding from the haemorrhoids.

The severity of the patient's general condition is determined by the rate of the blood loss rather than by its volume. It was shown in human experiments that maximum haemodilution occurs 3 to 90 hours after the extraction of approximately 1.1 litres of blood. It proceeds from this that the blood haemoglobin content does not reflect the severity of the blood loss. Measurement of the plasma volume in the first hours after the haemorrhage yields results that are more reliable. Immediately after the blood loss, the rate of cardiac contractions slows down and tachycardia develops later. After the occurrence of anaemia the hyperkinetic syndrome develops, the degree of which to a great measure determines the success of the therapeutic measures applied in this period.

After haemorrhage, the patient develops fever and azotaemia. Body temperature sometimes rises to 40°C and stays increased for several days and occasionally for even more than a week. Azotaemia develops only in bleeding from the parts of the gastro-intestinal tract localized proximal to the ileocaecal valve. In bleeding from the large intestine the content of non-protein nitrogen in blood

is normal. Schiff (1970) even suggests using this test for revealing the localization of the source of bleeding. Azotaemia and fever probably depend on the absorption of the products of blood digestion. Leucocytosis sometimes exceeding 15 000 always develops after haemorrhage. Thus, anaemia, leucocytosis, increase in non-protein nitrogen, and fever allow the diagnosis of bleeding to be made and its volume to be approximately determined. Treatment of bleeding cannot be successful if its cause is not identified.

Aetiology of Gastro-intestinal Haemorrhages

Bloody vomit and tarry stools are mostly encountered in diseases of the gastro-intestinal tract. They often occur in diseases marked by the syndromes of portal hypertension and shock. These gastro-intestinal haemorrhages must be differentiated from bleeding from the upper respiratory tract. Bloody vomiting also occurs in bleeding from the nose because blood entering the oesophagus along the posterior nasopharyngeal wall is swallowed. This possibility should be borne in mind in all cases when bloody vomiting occurs after nasal bleeding or after operations on the nasopharynx. The same is true of haemorrhages from the gums in severe scurvy. The differentiation of bloody vomiting from haemoptysis is discussed in the chapter 'Haemoptysis and Pulmonary Haemorrhage'.

According to the summarized statistics of different authors, gastric or duodenal ulcers are the cause of massive gastro-intestinal haemorrhage in 40 to 65 per cent of cases. Gastritis and varicose veins of the oesophagus and stomach are the cause of about equal frequency of massive bleeding. Gastritis, which is often complicated by acute erosions and ulcers, accounts for 11-12 per cent, and varicose veins for 9-18 per cent of all haemorrhages. The incidence of haemorrhages caused by oesophagitis and rupture of the oesophagus has noticeably grown in the last decade. Carcinoma of the stomach used to be among the common causes of haemorrhages. The diagnosis of this disease is now usually made long before it causes massive haemorrhage.

Gastric haemorrhages of other aetiology are rare and should be referred to the category of extremely rare clinical occurrences. Patients with gastro-intestinal haemorrhages arising in infectious diseases are not treated by internists for obvious reasons and are therefore excluded from differential diagnosis. Haemorrhages from acute and chronic gastric ulcers surpass all other haemorrhages in

frequency and that is why we have given them prominence in the differential diagnosis of all haemorrhages.

The diagnosis of gastro-intestinal bleeding is usually made easily if the patient has bloody vomiting and a tarry stool. Unfortunately, these vivid diagnostic signs sometimes appear only on the second or third day of the disease. This is explained by the retention of blood in the intestine where it may remain even till the patient dies. The absence of a tarry stool or bloody vomiting does not exclude gastro-intestinal bleeding, at least at the time of the patient's examination. Although bloody vomiting and a tarry stool may be discovered by the patient himself or his relatives, we may nevertheless speak of gastro-intestinal bleeding only after our own examination of the faeces and vomit. It should again be emphasized that some drugs (e.g. iron, bismuth) are capable of staining the faeces, whereas others (e.g. licorice) render it colourless.

Questioning the patient about the drugs which he takes is also very important from another point of view. The regular intake of some drugs often results in the formation of acute erosions and ulcers of the stomach. Acute gastro-intestinal bleeding may be their first clinical manifestation. This is particularly often encountered in patients given corticosteroids, acetyl salicylic acid, Butadione (phenylbutazone), Indocide (indometacin), or Rauwolfia. Chronic ulcer of the stomach and duodenum is usually marked by a characteristic combination of the pain and dyspeptic syndromes. A detailed questioning about a history of bloody vomiting or tarry stool, pain experienced before meals, vomiting after a meal, heartburn, nausea, eructation, or regular intake of sodium bicarbonate may reveal characteristic symptoms of peptic ulcer which the patient failed to mention because of emotional stress usually experienced during gastro-intestinal bleeding.

Diseases of the Stomach and Duodenum

Without denying the importance of questioning the patient in making the diagnosis of peptic ulcer it should nonetheless be pointed out that massive bleeding from the ulcer is very often a complete surprise for the patient himself. According to Bova (1967), in 15.3 per cent of patients profuse haemorrhage was the first clinical manifestation of peptic ulcer. They had formerly never applied for medical aid and had never noted any signs of the dyspeptic syndrome. Unfortunately, massive gastro-intestinal bleeding may be the first clinical symptom not only of ulcers, but of many other internal diseases.

Physical examination is of immense aid to the physician due to its negative rather than its positive results. It makes it possible to rule out perforation of an ulcer and disclose signs indicating the possible connection of the gastro-intestinal bleeding with other diseases. The diagnosis of ulcerous bleeding may be proved by arteriography. The contrast medium injected into the coeliac artery is found in the stomach in the form of a residual contrasting shadow. Thus, arteriography discloses the site of the bleeding which makes it much easier to plan therapeutic measures.

X-ray examination of the stomach is now conducted both at the time of the bleeding and soon after it has been arrested. X-ray is even recommended when the ulcerous origin of the bleeding raises no doubts, because it allows a topical diagnosis of the ulcer to be made and other diseases which may be important for judging the source of bleeding (e.g. diaphragmatic hernia, varicose oesophageal veins, duodenal diverticulosis) to be revealed.

X-ray demonstrates a filling defect in 85-92 per cent of cases with peptic ulcer. In some cases it is impossible to reveal the characteristic filling defect because the swollen mucosa overhangs the ulcerous crater or because the crater is closed with mucus or a blood clot. It is very hard to disclose retrobulbar ulcers and peptic ulcers of an anastomosis.

Gastro-intestinal haemorrhages in **gastritis** and sometimes in persons with an intact gastric mucosa may be a complication of acute erosions or ruptures of the oesophageal or gastric mucosa (the Mallory-Weiss syndrome) in some cases or develop through diapedesis in others. These sources of bleeding cannot be disclosed by X-ray examination. Gastroscopy is recently applied for their detection. Acute erosions heal within two or three days after the bleeding, and in order to reveal them gastroscopy must be performed in this period of time.

Sokolov (1975) studied the characteristic features of the endoscopic picture of the gastro-intestinal tract on the basis of extensive material. Endoscopy carried out in the first days after bleeding makes it possible to discover superficial lesions of the oesophageal, gastric, and duodenal mucosa which cannot be demonstrated by X-ray. Endoscopy also proves to be indispensable when X-ray reveals multiple lesions each of which could be the source of the bleeding (e.g. gastric ulcer and diaphragmatic hernia, duodenal ulcer and varicose oesophageal veins). Endoscopy makes it possible not only to establish the diagnosis in such cases, but also to determine the source of the bleeding. In accuracy, endoscopic diagnosis considerably surpasses all other methods of examination of the sources of gastro-intestinal haemorrhage. On the basis of extensive and comprehensively examined material compiled by Sokolov (1975), the correct cause of gastro-intestinal bleeding in 48.5 per cent

of cases proved possible to be established only by endoscopy.

Massive gastroduodenal bleeding results from erosions of the arterial wall. This complication does not, without any doubt, belong to the group of early signs of **carcinoma of the stomach**, but in some cases it proves to be its first clinical manifestation. This is also true of diseases encountered more rarely (carcinoma of the duodenum and carcinoma of the major duodenal papilla).

Detailed questioning of the patient sometimes reveals that he had suffered from dyspepsia and complains of indefined pain in the abdomen. Quite often even this cannot be disclosed because early stages of carcinoma may cause no disturbances in the patient's condition. Cachexia and a palpable tumour appear in the later stages of the disease. They make it easier to divulge the cause of the gastro-intestinal haemorrhages and at the same time testify to the lost opportunities for timely diagnosis of the disease. Preoperative diagnosis of a malignant tumour of the stomach in such cases may be trustworthy only after X-ray examination and in some instances after endoscopy of the stomach and duodenum.

Endoscopy of the stomach and duodenum combined with X-ray examination are the only reliable methods for establishing the diagnosis of gastric polyps and duodenal diverticula, which may also be the source of massive bleeding.

Erosive ulcerations of the gastric and duodenal mucosa, isolated or combined with gastritis and duodenitis, are among the frequent causes of gastro-intestinal bleeding. The erosive lesions are usually localized in the pyloroantral part of the stomach or in the duodenal bulb. They are found much less frequently in the fundus of the stomach. If it is suspected that gastritis is the cause of the bleeding, examination of the patient may be begun with endoscopy of the stomach. Lacking such assurance, the physician should first perform X-ray examination.

Circulatory disorders of the type of cardiogenic shock or thromboembolism of the pulmonary artery with severe arterial hypotension are often complicated by the development of erosions and acute ulcers of the stomach which, in turn, become the cause of massive bleeding. The patient's grave condition is no absolute contraindication for X-ray examination or endoscopy. The diagnosis of this complication is established in different departments for internal diseases without any difficulty when massive bleeding appears during shock or soon after it terminates. Massive haemorrhage is sometimes encountered in severe right-ventricular failure as a consequence of long-term ischaemia of the gastro-intestinal tract associated with centralization of circulation.

Acute erosions and acute ulcers of the stomach and duodenum are also encountered in traumatic shock, in burn shock and after serious and prolonged operations on the abdominal organs. Dia-

pedetic haemorrhages sometimes develop in the last instance.

Massive gastro-intestinal bleeding sometimes proves to be a complication of **diverticula of the stomach, duodenum, jejunum** or **colon.** Diverticulum of the stomach is a rare disease. It is usually localized on the posterior cardial wall and is manifested by the dyspeptic and pain syndromes indistinguishable from those occurring in peptic ulcer. Bleeding usually occurs from an eroded vessel in the wall of the diverticulum which had undergone inflammatory changes.

The identification of the cause of such haemorrhage is no easy task. It is most difficult to establish the diagnosis of gastric diverticula because the roentgenologist and clinician rarely happen to think of this disease. These diverticula, however, can only be detected if the physician has them in mind. Questioning of the patient and the results of physical examination usually provide no clue to the diagnosis of this disease. A diverticulum is demonstrated on X-ray as a mobile, positive shadow with clear-cut even outlines, which communicates with the cavity of the stomach usually by mean of a narrow neck. Endoscopic examination is conducted after the stomach is inflated. This makes the diagnosis of the diverticula much easier because inflation of the stomach contributes to the dilatation of the opening into the diverticulum.

Duodenal diverticula are encountered in approximately 2 per cent of cases examined by X-ray. They are usually localized in the bulb, the upper horizontal, the upper and middle third of the descending part of the duodenum. They often cause no disturbances in the patient's subjective condition and are revealed by chance during X-ray examination for some other reason. The formation of diverticula is attended by clinical syndromes: biliary colic, intestinal obstruction, perforation, pancreatitis and gastric ulcer.

Sometimes an ulcer forms inside the duodenal diverticulum and may be complicated by gastro-intestinal bleeding. According to Zemlyanoi (1970), haemorrhage is encountered in approximately 1 per cent of patients with duodenal diverticulosis. The bleeding may be profuse or occult. X-ray examination, particularly if carried out under conditions of artificial duodenal hypotension, makes it possible to detect diverticula in it. The source of bleeding remains unrecognized. Endoscopy of the duodenum not only reveals the diverticula, but discloses their association with the bleeding. The role of these findings in planning the therapeutic measures cannot be overestimated.

Diverticula of the small intestine are extremely rare. They may also be complicated by bleeding, which results from ulceration of the mucous membrane of the diverticulum or erosion of a blood vessel stretching in its wall.

Meckel's diverticulum is a frequent developmental anomaly of the gastro-intestinal tract. **Ulcer of Meckel's diverticulum** develops when there are areas producing pepsin and hydrochloric acid in its mucous membrane. Massive bleeding may be a complication of this ulcer. Bleeding from Meckel's diverticulum usually occurs in childhood or adolescence. It may be slight or massive. In a moderate rate of bleeding, the blood has time to disintegrate in the ascending colon and turns black. Melaena is followed by the discharge of thin blood with dark cherry-coloured clots. At a high rate of bleeding, scarlet blood is discharged. Recurrence is a characteristic feature of bleeding from Meckel's diverticulum.

Intestinal bleeding in ulcer of Meckel's diverticulum may develop in attendance to long-existing dyspeptic and pain syndromes typical of peptic ulcer or may occur suddenly in sound health. In the former case it is mistaken for bleeding from a duodenal ulcer, in the latter case for bleeding in haemorrhoids, telangiectasia, ulcerative colitis or ileus. The differential diagnosis with these diseases is very difficult. Blood discharged from the rectum in ulcerative colitis, ileus or dysentery always reveals an admixture of mucus. Pure blood is discharged in bleeding from Meckel's diverticulum. Abdominal pain in ileus occurs in attacks and always begins prior to bleeding. In bleeding from Meckel's diverticulum, no pain may be experienced in the abdomen or it may appear after the bleeding. It is of mild intensity as a rule.

Diverticula of the colon are usually multiple. They are found in 5 to 10 per cent of persons over the age of fifty. Diverticula of the sigmoid colon take first place in frequency. They account for 80-90 per cent of all diverticula of the colon. They may be asymptomatic or may be complicated by inflammation, bleeding or perforation, or malignant degeneration to carcinoma. The clinical picture may be of a great variety. Intestinal haemorrhage in diverticula of the colon may be profuse or occult. The direct cause of the bleeding is established with difficulty. Colonoscopy and examination by means of a contrast enema are necessary for its identification.

Bloody vomiting and tarry stool are observed at periodic intervals in **congenital telangiectases** of the stomach and intestine. The disease is familial and is inherited as a dominant trait. The medical history is very important in making the diagnosis. The patient's parents or close relatives also have recurrent haemorrhages. In inspection attention must be focused on the condition of the oral, lip and nasal mucosa. Telangiectases are often found here in great numbers. They are found less frequently on the skin than on the mucous membranes, probably because the skin is rarely inspected so scrupulously as the mucous membranes. Many cases have been described with bloody vomiting occurring as a consequence of bleeding from telangiectases located in the mucous membrane of the cardia.

Endoscopy is the only method by means of which bleeding telangiectasis may be disclosed.

Gastro-intestinal bleeding may be a complication of **hereditary atrophy of elastic tissue** of the body (pseudoxanthoma elasticum). The disease is usually manifested by skin and eye lesions. Atrophy of elastic tissue in the wall of arteries found in the submucosal coat of the stomach may lead to massive bleeding. A tentative diagnosis of pseudoxanthoma elasticum is made from the findings of physical examination. Atrophy of the elastic tissue develops earliest on the neck, in the cubital and axillary folds, on the face, and in the inguinal folds. Simultaneous findings are vascular retinal lesions and the syndromes of mitral stenosis or mitral insufficiency often in combination with signs of aortic insufficiency.

Bleeding into the biliary tract occurs in injuries to the liver, after biopsy of the liver, in rupture of an aneurysm of the hepatic artery or its branches, and in rare cases in injuries inflicted by a stone passing along the biliary tract. Blood from the biliary tract enters the duodenum. Pain in the right hypochondrium is felt at first and then joined by jaundice, bloody vomiting or a tarry stool. Milder cases are only manifested by occult blood in the faeces. It is extremely difficult to establish the diagnosis of haemobilia. Aneurysm of the hepatic artery or its branches is best demonstrated by contrast arteriography.

Diseases of the Oesophagus

In 1929 Mallory and Weiss described massive gastro-intestinal haemorrhage which occurred after vomiting and which was associated with linear rupture of the gastric mucosa close to the gastro-oesophageal junction. For a very long time the diagnosis of the Mallory-Weiss syndrome was only established during operation or autopsy. With the introduction into practice of endoscopic methods of examination it became possible to make the diagnosis of this syndrome without an operation.

The common anatomic basis of the Mallory-Weiss syndrome is linear rupture of the mucous membrane of the lower third of the oesophagus or cardia or simultaneous rupture of the mucous membrane of both organs. In the last instance the line of the rupture b gins in the lower oesophagus, crosses the gastro-oesophageal junction and ends in the stomach. In rare cases the rupture spreads to the submucosal coat. The other coats remain intact.

A sufficient number of facts have been accumulated to date indicating that, in addition to severe forms, mild forms of the syndrome also occur. Patients recover from them without surgery and even

without transfusion of blood. The Mallory-Weiss syndrome accounts for about 4.5 per cent of all cases of gastroduodenal haemorrhages (Watts and Admirand, 1974). They are encountered particularly often in alcoholism, in patients suffering from an attack of seasickness or after recurrent attacks of severe vomiting during airflight or during pregnancy. The bleeding is slight, as a rule, and usually does not call for an emergency surgical intervention.

The disease begins with an attack of severe cough or vomiting which soon turns bloody. In some cases melaena occurs just before bloody vomiting. Gastritis is found in about half of patients with the Mallory-Weiss syndrome and hiatal hernia in another half.

A tentative diagnosis of the Mallory-Weiss syndrome may be made in every case of painless gastro-intestinal bleeding occurring immediately after a severe cough or recurrent vomiting (e.g. in toxicosis of pregnancy). The final diagnosis of mucosal rupture may only be established from the findings of endoscopy or during operation.

Gastro-intestinal haemorrhages in **diaphragmatic hernia** occur soon after incarceration of part of the stomach in the hernial opening. We did not encounter profuse gastric haemorrhages possibly because all patients with suspected incarcerated hernia were immediately sent for surgery. In all cases in our practice intensive epigastric pain occurred simultaneously with the gastric bleeding manifested by vomiting with an admixture of blood. The pain and gastric haemorrhage occurred after the patient had lifted some heavy weight, after tensing his muscles and other physical exertions attended by increased intra-abdominal pressure. This cause of gastro-intestinal bleeding is identified reliably by X-ray examination. After reduction of the diaphragmatic hernia, the gastric haemorrhage ceases but begins anew in recurrent herniation.

Repeated entry into the oesophagus of active gastric juice and other digestive enzymes may lead to the development of **peptic oesophagitis** (reflux oesophagitis). It is encountered in hiatal hernia, pyloric stenosis, gastric and duodenal peptic ulcer, cholecystitis, achylia and other diseases and syndromes. Erosions and, in some cases, ulcers too form on the swollen and hyperaemic oesophageal mucosa.

Occult bleeding occurs in every case of peptic oesophagitis. Massive haemorrhage is rarely encountered, and then mostly in patients suffering, besides, from hiatal hernia. The diagnosis of reflux oesophagitis may be presumed on the grounds of characteristic complaints of increased salivation, constant eructation of food or acid or bitter mucus, and painful swallowing. The final diagnosis is established from the findings of X-ray examination or endoscopy.

Carcinoma of the oesophagus almost always begins with dysphagia. Ulceration of the tumour usually leads to mild bleeding. Deep

oesophageal ulcers which sometimes penetrate the large blood vessels and even the aorta occur in some cases during disintegration of the carcinomatous tumour. Profuse and usually fatal bleeding into the oesophagus occurs in ruptures of the large vessels. There is usually no difficulty in identifying the cause of this bleeding because the signs of the principal disease, the oesophageal tumour, are clearly manifested by this time.

Bloody vomiting occurs in rupture of **aneurysm of the thoracic aorta** into the oesophagus and when a tumour arising from the mediastinal structures grows into the oesophageal wall. The growth of such a tumour is at first attended by compression of the mediastinal organs (bronchi and oesophagus). Compression of the large veins or growth of the tumour into them develops in attendance later and leads to dilatation of the subcutaneous veins of the upper trunk, oedema of the neck and upper limbs and their cyanosis. These changes are commonly vividly manifested more on one side than on the other. These signs allow a mediastinal tumour to be distinguished from carcinoma of the oesophagus and aneurysm of the thoracic aorta.

Portal Hypertension

Varicose veins of the oesophagus come second in frequency after gastro-intestinal ulcers as the cause of profuse gastro-intestinal bleedings. The veins of the lower third of the oesophagus are mostly affected. Dilatation of the veins of the cardia is often encountered simultaneously. The bleeding begins abruptly, continues turbulently and is distinguished by a tendency to recur. In all cases of massive haemorrhage examined by Patsiora (1974) its source was always a vein with a round opening of various diameters in its wall, sometimes with a thrombus protruding from it. Bleeding from dilated gastric veins is an extremely rare occurrence and is usually less massive.

Bleeding from dilated oesophageal veins must be first distinguished from ulcerous bleeding which is much more common and may be just as massive. The differential diagnosis presents no difficulty if in questioning the patient it is disclosed that he had suffered from peptic ulcer for many years and already had a history of bloody vomiting or melaena. The differential diagnosis is difficult when the gastro-intestinal haemorrhage is the first manifestation of peptic ulcer or gastritis. The results of physical examination and, if the patient's condition permits, the results of questioning are of immense help in such cases. Bleeding from the oesophageal veins

occurs in portal hypertension, as a rule, and is among its late complications. The other signs of portal hypertension are already developed by this time in most cases and may be detected on examination of the patient.

It is a general practice to distinguish suprahepatic, intrahepatic and extrahepatic forms of portal hypertension. In Pick's pseudocirrhosis signs of portal hypertension appear only in the late stages when both the patient's appearance and his general condition are so characteristic that the disease is easily recognized at the very first examination.

Nor is there any difficulty in making the diagnosis of biliary cirrhosis of the liver, haemochromatosis and other diseases of the liver the clinical picture of which forms before the oesophageal veins become dilated. Haemorrhages caused by cirrhosis of the liver, Chiari's disease and portal hypertension of extrahepatic genesis usually present a diagnostic problem.

Bleeding from the oesophageal veins occurs only in the late stages of cirrhosis of the liver and it is therefore important to determine the size of the liver and spleen on examination of the patient as well as look for signs of increased collateral circulation. After the bleeding begins these signs of portal hypertension are less manifested. The diminution of the spleen in size is particularly noticeable. This is why it is essential to find out whether or not the spleen had been enlarged prior to the haemorrhage and not to restrict the examination to palpation of its lower pole, but to determine its size also by percussion.

Characteristic muscular atrophy of the upper trunk is always encountered in the late stages of cirrhosis but is observed neither in peptic ulcer nor in gastritis. Enlargement of the spleen does not take place in every instance of cirrhosis of the liver, but if found, it should be considered quite a reliable indication that the patient has portal hypertension.

The dilated subcutaneous veins collapse during bleeding and may therefore be rarely valuable in differential diagnosis. The same is true of spider naevi. Under the effect of the bleeding, the signs of hepatic insufficiency become more manifest. Bleeding sometimes leads to the development of ascites, and even coma.

The functional state of the liver is obviously of great differential diagnostic importance. Whenever possible it is therefore advisable to test at least the blood bilirubin content, and, even better, the capacity of the liver to clear the blood of bromsulphophthalein, Bengal rose or azorubin S. Disturbance in the hepatic secretory function often occurs in cirrhosis of the liver but is not characteristic of haemorrhages of other origin. In a patient with icteric sclerae or skin, massive bleeding should be attributed to cirrhosis of the liver and not to diseases of the stomach or duodenum.

The sharply altered protein composition of blood serum with characteristic reduction in albumin concentration and increased gamma globulin content is encountered in only far-advanced cases of cirrhosis of the liver. In peptic ulcer and chronic gastritis the blood serum protein content does not change. Persistent abdominal pains in a patient with an ulcer usually disappear after the haemorrhage. Patients with cirrhosis of the liver are troubled by weakness and not by pain before the bleeding. After the bleeding they always become even weaker.

Massive gastro-intestinal bleeding often proves to be the first clinical manifestation of a group of diseases marked by the syndrome of extrahepatic portal hypertension. Thrombosis of the portal vein and its branches, their inflammation and congenital or acquired stenoses are included in this group. Inflammation of the portal vein usually develops after appendicitis, dysentery, cholecystitis or operations on the abdominal and pelvic organs. Some of these patients had suffered umbilical sepsis or an abdominal injury in childhood. The disease may follow a subclinical course for many years and be eventually manifested by bloody vomiting caused by bleeding from the dilated oesophageal veins. Quite often the patient has forgotten by this time that he had suffered an abdominal injury or complicated appendicitis and is inclined to believe that the bloody vomiting had occurred in sound health.

The spleen in patients with extrahepatic portal hypertension is always enlarged, and very considerably at that. Massive haemorrhages complicating thrombosis of the portal vein are sometimes attended by ascites which disappears simultaneously with the correction of anaemia. These patients have no complaints before the bleeding. In rare cases, knowing that their spleen is enlarged, they complain of heaviness in the left hypochondrium. Soon after the bleeding ceases they again feel ready for work. Ascites does not develop after bleeding from an ulcer. Most patients with peptic ulcer usually experience pain long before the bleeding begins.

Certain differential diagnostic importance should be attached to the results of blood tests. Bleeding in peptic ulcer and gastritis is attended by leucocytosis. Leucopenia is characteristic of the extrahepatic form of portal hypertension. In our experience, leucopenia did not disappear even after the haemorrhage in cases of this disease. This peculiar reaction of the bone marrow to haemorrhage is explained by hypersplenism under the effect of which the release of the young cells of the myeloid series into the peripheral blood is disturbed.

Extrahepatic portal hypertension is mostly encountered in young persons. Exception to the rule are patients with polycythaemia in whom thromboses in the portal vein system are encountered both in middle age and when they are older. The differential diagnosis

in this case is not very difficult because the diagnosis of the principal disease is made long before the thromboses have time to develop.

Splenoportography, laparoscopy and scintiphotography of the liver and spleen are usually conducted after the massive bleeding ceases. With these methods of examination portal hypertension can be differentiated from peptic ulcer. Pressure in the portal vein is increased in all forms of portal hypertension but is normal in peptic ulcer. The size of the liver and spleen and the appearance of the surface of the liver and its colour found on laparoscopy permit the diagnosis of portal hypertension to be made with assurance and to clarify its role in the genesis of massive haemorrhage.

Diseases of the Intestine

Gastro-intestinal haemorrhage with the discharge from the rectum of scarlet blood of jelly-like consistency or in clots indicates that the blood had no time to be affected by the digestive juices. This is encountered either in markedly increased motor function of the intestine or in bleeding from the colon. The former happens only in massive haemorrhage from the upper parts of the gastro-intestinal tract which usually leads to acute anaemia, is often attended by bloody vomiting and is sometimes complicated by shock. Haemorrhage from the colon is rarely massive. Moreover, it is not attended by bloody vomiting. Haemorrhoids are the most common cause of bleeding from the anus, but to be sure that this is the responsible factor and to exclude all other causes, it is necessary to conduct systematic examination of the entire colon.

Blood flowing from haemorrhoids or anal fissures is not mixed with the faecal matter. Mucus is either not found in the faeces or is present in negligible amounts. If the blood is mixed with mucus or faeces, the case is most probably that of carcinoma or polyp of the large intestine and not of haemorrhoids. Blood is discharged from the anus in polyps and malignant tumours of the rectum and colon and in diseases marked by the formation of ulcers on their mucous membrane.

Most **polyps** discovered by the routine clinical methods of examination are localized in the rectum and distal part of the sigmoid colon. According to pathologists, they are mostly found in the caecum (Bockus, 1976). The polyps usually grow on a thin pedicle 2-3 cm long and have a soft surface. It is difficult to detect them by digital palpation. Most of them are found during proctosigmoidoscopy. The mushroom-like surface of the polyps tends to become inflamed and bleeds. According to some authors, the frequency of haemorrhages

from a polyp ranges from 4 to 70 per cent. Polyps localized more distally may be detected during proctoscopy and X-ray examination with the use of a contrast enema. Villous polyps are encountered most frequently in elderly persons. They are rarely complicated by haemorrhages but often lead to the development of hypokaliaemia consequent upon the loss of mucus for the most part. A considerable amount of bloody mucus is discharged in cases with multiple polyps. Massive intestinal haemorrhages are rare.

Malignant tumours of the colon are usually found in middle-aged and elderly persons. The first sign is a disturbance in the patient's regular intestinal activity with the development of diarrhoea or constipation. Sometimes they alternate. Anaemia caused by blood loss from the surface of the growing tumour develops somewhat later. In most cases these blood losses are negligible and the blood mixes with the faeces and merely changes the colour of the stool. The stool becomes dark when the tumour grows in the right half of the colon.

Carcinoma in the left half of the colon is usually marked by circular spread and causes stenosis of the intestine in the early stages. This leads to stasis of the contents in the dilated segment of the intestine proximal to the site of its stenosis. X-ray examination of the colon by means of a contrast enema easily discloses these disorders. Clinical examination in this period of the disease usually reveals borborigmus above the site of the stenosis and alternation of constipation and diarrhoea. Blood losses from the surface of the tumour localized in the left half of the colon are manifested as admixtures of red blood on the surface of the faeces.

The development of foci of necrosis and inflammation in the growing tumour induce a febrile reaction. Pain appears if the tumour grows into the peritoneum. Anorexia and loss of body weight are noted by this time. The appearance of blood in the faeces is therefore a late sign of carcinoma of the colon. Massive blood losses are rare.

Recurrent intestinal bleeding may be the only clinical manifestation of **ulcerative colitis.** If these haemorrhages are combined with more or less severe constipation, they are often mistaken for bleeding from haemorrhoids at first. The general condition of some patients is sometimes quite satisfactory. The true cause of the haemorrhages is disclosed only after failing to find haemorrhoids by digital examination the physician resorts to proctosigmoidoscopy during which he finds changes in the mucous membrane characteristic of ulcerative colitis.

In severer ulcerative colitis with involvement of the rectum and sigmoid colon, blood losses from the rectum are regular. Diarrhoea with the discharge of blood and mucus is usually encountered. The stool consists of formed faecal matter at times, but the patient often

experiences tenesmus during which only blood and mucus, usually in small amounts, are discharged. The appetite and body temperature are normal. The patient retains his usual body mass, but complains of rapid fatiguability.

In severe ulcerative colitis with involvement of most of the colon, the stool is always liquid and the blood, mucus and faeces are mixed. Often only blood is discharged. The urge to defaecate becomes imperative which makes the patient keep within close proximity to toilets or to know their whereabouts on the way to his work. Abdominal pain is often encountered and is particularly intensive before the stool is passed. Anorexia and severe diarrhoea are usually attended by fever and the development of body mass deficiency the extent of which correlates well with the severity of the disease.

Haemorrhages in chronic ulcerative colitis are rarely massive, but in an acute onset of the disease and in its fulminant forms the bleeding may be so intense that a clinical picture of shock develops. The severity of the shock is undoubtedly determined not only by the volume of the blood loss, but by the disorders of water-electrolyte metabolism and the toxicosis developing in association with a concomitant infection.

Intestinal haemorrhages in **Crohn's disease** with involvement of the small intestine are encountered in approximately 13 per cent of cases, but are massive only in 2.3-4.8 per cent. In granulomatous colitis, moderate intestinal haemorrhages are encountered in about 50 per cent and profuse haemorrhages in 4 per cent of cases. Haemorrhage from the rectum is a late complication of Crohn's disease. It is encountered only when the principal diagnostic triad of the disease (abdominal pain, diarrhoea and loss of body weight) is manifest. Red blood is found in the faeces in approximately 3 per cent of patients who had applied to their doctor for the first time. It would be oversimplifying to say that any intestinal bleeding in a patient with ulcerative colitis or Crohn's disease is a manifestation of the principal disease. These haemorrhages may be a consequence of its complications, e.g. haemorrhoids or carcinoma. Complete examination of the patient must therefore be carried out in every case of intestinal bleeding.

Pure blood is discharged from the anus in amoebiasis, bacillary dysentery and balantidiasis. Intestinal bleeding is particularly characteristic of **amoebiasis.** In most cases this disease sets in as mild diarrhoea, but particularly severe cases begin suddenly with sharp abdominal pain which is joined by diarrhoea with frequent discharge of large amounts of mucus mixed with blood or of pure blood. A correctly made diagnosis and adequate treatment usually ensure the patient's total recovery in two or three weeks. If not recognized, the disease takes a chronic course the anatomical foundation of which are chronic intestinal ulcers or amoebomas. The

clinical picture of the disease is no different from that of ulcerative colitis. The stool may be passed from six to eight times daily. Relatively small amounts of blood and mucus are usually discharged. In particularly severe cases, blood and mucus are discharged instead of faecal matter. Just as non-specific ulcerative colitis, amoebiasis is marked by alternation of exacerbations and remissions.

Balantidiasis is characterized by the formation of ulcers on the mucous membrane of the large intestine. Infection is usually mild, so that the disease takes the form of mild or moderately severe diarrhoea in which the periods of exacerbation are replaced by long-term remissions under the effect of dietetic treatment. The stool is loose and contains much mucus, sometimes with an admixture of blood. Intestinal haemorrhages are usually not encountered in balantidiasis. The disease is contracted by persons who come in contact with pigs. In the Soviet Union this is a rare disease.

In the USSR **bacillary dysentery** is mostly caused by *Shigella flexneri* and *Shigella sonnei*. A particularly severe form of the disease develops in infection by *Shigella shigae*, whose exotoxin affects not only the mucous membrane of the intestine, but its nerve structures. Blood, pus and mucus are discharged in severe diarrhoea. A stool with tenesmus and false urges may occur more than 10 to 12 times daily. The disease is usually marked by severe toxicosis.

In the past when tropic malaria had still not been eradicated in the Soviet Union, cases of this disease complicated by intestinal haemorrhage were encountered.

Tuberculous enterocolitis and tuberculous ulcers of the small or large intestine are encountered much less frequently now than before World War II. Intestinal bleeding is found in about 4 per cent of cases of tuberculous enteritis. The low incidence of haemorrhages is explained by the development of obliterating endarteritis in the tissues around the ulcer. The clinical picture of intestinal tuberculosis is not specific and only a tentative diagnosis may be made on the basis of the clinical signs.

Loss of body weight and abdominal pain are the most common clinical manifestations of tuberculosis of the intestine. The abdominal pain intensifies noticeably after a meal and nausea appears and often terminates in vomiting. Peristalsis intensifies clearly and in about 50 per cent of the patients it may be heard at a distance after a meal. Diarrhoea is infrequent, but once it appears, it is continuous. Mucus is often seen in the stool, but an admixture of blood is rarely found. With the appearance of steatorrhoea the stool acquires a characteristic sharply sour odour. Abdominal palpation elicits tenderness, usually in the ileocaecal region, the favoured site of tuberculous lesions of the intestine.

The intestinal contents pass much more rapidly through the inflamed intestinal segments than through the adjoining healthy seg-

ments. During X-ray this is recognized from the accumulation of the barium suspension proximal and distal to the inflamed intestinal segment. Because of increased excitability of the affected segment of the intestine, the contrast medium is not retained in it. The poorly filled distal segment of the ileum in combination with the accumulation of barium in its proximal part and in the caecum is an important X-ray sign of terminal ileitis. Simultaneous affection of the caecum is encountered only in tuberculous ileotyphlitis as a rule.

In summing up the abovestated, it can be said that intestinal haemorrhage may be massive or moderate. Blood discharged from the anus may be dark or red. This may be pure blood or blood with an admixture of mucus and pus. The admixture of mucus or pus is the only sign which makes it possible to reliably distinguish bleeding from the terminal segment of the ileum and colon from bleeding from the oesophagus and upper part of the gastro-intestinal tract. Intestinal haemorrhage is encountered in many diseases and particularly frequently in ulcerative colitis, Crohn's disease, and carcinoma, polyps, diverticulitis and tuberculosis of the intestine. A tentative diagnosis is made in each of these diseases on the grounds of interrogation and the results of physical examination. Special methods of examination often have to be applied in establishing the final diagnosis.

After intestinal bleeding is recognized in the patient, it is necessary to question him about the beginning and duration of the disease. Intestinal bleeding is one of the typical initial symptoms of non-specific ulcerative colitis. Ulcerative intestinal lesions of parasitic origin usually set in gradually. They are at first often mistaken for mild gastroenteritis caused by food that is not fresh. Only unsuccessful treatment without professional advice and the appearance of blood in the stool make the patient finally call on a doctor. An insidious beginning is also characteristic of Crohn's disease and carcinoma of the large intestine. Intestinal haemorrhage is a late manifestation in such cases. It is likewise important to take the patient's age into account. Crohn's disease and non-specific ulcerative colitis are suffered by young and middle-aged individuals, whereas haemorrhoids, diverticulitis, carcinoma and polyps of the intestine are usually the lot of the elderly.

Examination of the perineum and rectum discloses haemorrhoids, anal fissures, pararectal fistulae and perianal affection of the skin characteristic of Crohn's disease. Endoscopy of the rectum and sigmoid colon allows their diphtheritic lesions characteristic of bacillary dysentery to be distinguished from lesions typical of ulcerative colitis. The rectal mucosa is involved in every case of non-specific ulcerative colitis, moreover far more severely than the other parts of the large intestine. The alternation of inflamed mucosal areas

with areas normal in appearance is a pathognomonic sign of Crohn's disease.

Ulcers in amoebiasis are already diagnosed during examination because of their characteristic appearance. Of high diagnostic importance are also the results of microscopy of smears taken from the floor of such an ulcer and the findings of biopsy of the edges of the ulcer, pseudopolyps and mucosal areas which are normal in appearance. The discovery of granulomas, *Mycobacterium tuberculosis*, amoebas or balantidia organisms in the preparation substantiate the diagnosis of Crohn's disease, tuberculosis or parasitic ulcer of the large intestine, respectively. The search for protozoa in smears prepared from warm faeces, and inoculation of nutrient media with faeces for the isolation of pure cultures of dysentery bacilli or *M. tuberculosis* may be of immense aid in identifying the cause of intestinal bleeding. The X-ray method for examination of the intestine and the methods of the interpretation of results are discussed in detail in the chapter 'Diarrhoea'.

Other Diseases

Bloody vomiting and tarry stools are sometimes encountered in **haemorrhagic vasculitis** which is usually found in males between the ages of 10 and 30. In the most commonly encountered variant, this disease begins with fever and purpura which are soon joined by arthralgia and arthritis. Body temperature may be elevated to 39-40°C at the onset of the disease. Affection of the skin is manifested by purpura or erythema. Petechiae, erythema and ecchimosis usually appear simultaneously. The eruption may occur on any part of the body, but is found most frequently on the lower limbs. Moderate pain in the joints of the lower limbs is encountered in almost every case of the disease. Polyarthritis with sharp pain is rare. Abdominal pain is usually moderate in this form of haemorrhagic vasculitis.

Haemorrhagic eruption in which abdominal pain predominates in the clinical picture is a much less frequent occurrence. The pain is caused by haemorrhages into the submucosal coat of the small intestine. It occurs in attacks, as a rule, and is attended by recurrent vomiting. The clinical picture resembles that of ileus. Bloody vomiting and a tarry stool usually appear within the first hours after the onset of the disease. Body temperature may be normal, although in rare cases it is elevated. The other signs of haemorrhagic vasculitis (affection of the joints and kidneys, purpura) develop in attendance to bloody vomiting later and may be absent at the time when the doctor should reach a decision on the cause of the bloody vomiting.

Diagnostic difficulties are definitely not so great when special attention is focused at the following three signs. A tarry stool in massive ulcerous bleeding or in bleeding from dilated oesophageal veins is always homogeneous; it consists of blood. A tarry stool in haemorrhagic vasculitis consists of blood with an admixture of mucus. This important detail will be immediately detected by the doctor if he examines the stool himself. Moreover, bloody vomiting and melaena in haemorrhagic vasculitis occur simultaneously with pain in the abdomen. Abdominal pain is not experienced in portal hypertension whereas in peptic ulcer it disappears immediately after the bleeding begins, as a rule. Haemorrhagic vasculitis occurs in the recurrent attacks of the disease at more or less considerable intervals of sound health. Questioning the patient about attacks of purpura with polyarthritis suffered in the past can make it much easier to identify the cause of gastro-intestinal bleeding.

The kidneys are affected more frequently in the abdominal syndrome than in other forms of haemorrhagic vasculitis. Proteinuria and haematuria often occur in gastro-intestinal haemorrhages caused by haemorrhagic vasculitis but are not characteristic of massive haemorrhage in ulcer, gastritis and portal hypertension. Urinalysis is just as important as a blood test in the differential diagnosis of gastro-intestinal haemorrhage.

Bloody vomiting and melaena are occasionally observed in **thrombocytopenic purpura** both in the idiopathic and the acquired (secondary) forms. Two forms of idiopathic thrombocytic purpura are distinguished, chronic and acute. The chronic form usually begins in childhood or during puberty. It is characterized by an undulant course with the alternation of exacerbations and remissions. The duration of these periods varies noticeably from one case to another. The blood platelet count usually falls below the critical level of 60 000 per 1 μl in the period of exacerbation. The qualitative filling of the platelets is noted simultaneously. This is clinically manifested by purpura on the skin and mucous membranes of the mouth, nose, intestine and less frequently of the urinary and genital tracts, and by bleeding from the mucous membranes.

The acute form of idiopathic thrombocytopenic purpura begins all of a sudden. A healthy person develops fever abruptly during which copious purpura appears on the skin and mucous membranes. Mild attacks of the disease cease within a few days, whereas severe attacks may terminate in death or take a chronic course. The characteristic signs of the disease are thrombocytopenia and purpura with bleeding from the mucous membrane of the nose, mouth, intestine, uterus, vagina, renal pelves and ureters. Bloody vomiting develops either because blood flowing from the upper respiratory tract is swallowed or because the stomach is overfilled with blood

from the vessels of its mucosa. Melaena occurs in bleeding from the vessels of the small intestine.

No difficulty arises in identifying the cause of gastro-intestinal bleeding in cases of chronic thrombocytopenic purpura because the patient is usually well aware of the principal disease from which he is suffering, while the copious nasal bleeding and skin purpura tell the physician that this is an exacerbation of the disease. It is far more difficult to make the diagnosis in acute cases of the disease. The extravasations and ecchimoses on the skin and mucous membranes may be very moderately pronounced or may appear later than the bleeding from the gastro-intestinal mucosa. A diagnostic error may be avoided if the signs of purpura are sought purposefully in every case of gastro-intestinal bleeding and tests for coagulation of the blood and a blood platelet count are made.

In questioning the patient about his life and health special attention must be paid not only to the history of purpura, but to the possible association of the present and past exacerbations of the purpura with the intake of drugs. Marked thrombocytopenic purpura is particularly common in treatment with quinine, quinidine, sulphanilamides, barbiturates and preparations of gold and arsenic. Symptomatic thrombocytopenic purpura usually underlies bloody vomiting and melaena in leucoses. The diagnosis of bloody vomiting and melaena is easily made in patients with haemophilia, uraemia and lymphogranulomatosis, because they are encountered only in manifest cases of these diseases and are their late complications.

Supplement XI-1

Causes of Gastro-intestinal Haemorrhage

1. Diseases of the stomach and duodenum.
   Chronic ulcer.
   Acute erosions and ulcers.
   Acute gastritis and duodenitis.
   Tumours.
     Carcinoma.
     Polyps.
   Incarcerated diaphragmatic hernia.
2. Diseases of the oesophagus.
   Carcinoma.
   Peptic ulcer.
   Peptic oesophagitis.
   Rupture (Mallory-Weiss syndrome).
   Varicose veins (in portal hypertension).
3. Diseases of the intestine.
   Degenerative.
     Vascular ectasias.
     Diverticulosis.

Inflammatory.
Chronic ulcerative enteritis.
Tuberculous ileotyphlitis.
Crohn's disease.
Colitis.
Non-specific ulcerative.
Protozoal.
Bacterial.
Haemorrhoids.
Tumours.
Malignant.
Benign.
Polyposis.
Ulcer of Meckel's diverticulum.
4. Other diseases.
Haemorrhagic vasculitis.
Thrombocytopenic purpura.
Thrombosis of the mesenteric artery.
Telangiectasias.
Congenital.
Acquired.
Haemobilia syndrome.
Scurvy.
Pseudoxanthoma elastica.

Chapter XII
Goitre with Thyrotoxicosis

The thyroid gland moves in the act of swallowing together with the larynx and even its slight enlargement is therefore easily disclosed by inspection or palpation. Marked enlargement of the gland leads to stridulous breathing because the trachea and larynx are compressed. Paresis of the vocal cords is sometimes noted. The voice changes only in paresis of both cords. Paresis of only one cord is usually detected only during laryngoscopy. Compression of the oesophagus is marked by dysphagia.

In some diseases the thyroid does not move during the act of swallowing. It may be localized partly or completely behind the sternum and compress the adjacent vessels and organs of the anterior mediastinum. Compression of veins is a particularly frequent occurrence and is manifested by a subcutaneous network of venous collaterals on the neck. The size and localization of the thyroid are determined most accurately by means of isotope or ultrasonic scanning. Enlargement of the thyroid is observed both in healthy individuals and in the gravely ill.

Diffuse, Nodular and Mixed Goitre

In most cases, thyrotoxicosis is a consequence of one of the following three diseases: diffuse toxic goitre, toxic adenoma, and toxic multinodular (microfollicular, mixed) goitre (Supplement XII-1). These diseases are easily distinguished by clinical methods of examination or isotope scanning of the thyroid. Unfortunately, there are still many other causes of thyrotoxicosis besides those mentioned here without the identification of which the therapeutic measures applied by the doctor often fail.

Goitre, exophthalmos and tachycardia are considered the principal symptoms of thyrotoxicosis, particularly in patients with diffuse toxic goitre. The condition prevails among females between the ages of 20 and 40. These young, and for the most part charming women turn to the doctor because of weakness, easy fatiguability, poor tolerance of heat, palpitation and irritation, which had appeared only a few months previously.

The doctor usually sees a graceful woman with large, widely opened glistening eyes. Examination reveals a warm slightly moist skin,

tachycardia, tremor and a small diffuse goitre. The inconstancy of this last sign should be borne in mind. Scintigraphy demonstrates a thyroid gland of normal size in 1-3 per cent of patients. Tachycardia is also frequent though not an obligatory sign of thyrotoxicosis.

In graver cases, cachexia develops whereas the appetite remains normal or even increases and there are exophthalmos and other ocular signs: rare blinking, lagging of the upper eyelid when the patient looks down, deficient convergence, and hyperpigmentation of the eyelids. Irritability, tears without cause, and muscle weakness appear. The strength of the proximal muscles of the limbs is particularly sharply reduced as a result of which patients feel unsteady in their knees and are often incapable of holding dishes. Muscle weakness is sometimes so intense that it has to be differentiated from other myoplegic syndromes. Far-advanced cases are marked by protracted fever (which, according to our experience, may be as high as 38.5° C) and the thyrotoxic heart and malabsorption syndromes.

A less known although no less frequent sign of the disease is gynaecomastia, described by Basedow as early as 1840. Onycholysis (separation of the nail from the nailbed) is encountered in approximately 13 per cent of patients. Pretibial oedema develops in almost 50 per cent of patients given treatment for thyrotoxicosis. Skin hyperpigmentation closely resembling that in Addison's disease occurs in some cases of thyrotoxicosis. Its underlying factor is hypocorticism.

Central and paracentral scotoma develops once in a while in Basedow's disease. The patient gradually becomes blind within several weeks, after which vision is partly or completely restored. Oedema of the subcutaneous tissue with no concomitant signs of heart failure sometimes develops. Vomiting, constipation, increase in body weight, hepatitis, osteoporosis and acute thyrotoxic encephalopathy are among the rare manifestations of Basedow's disease.

Toxic adenoma usually appears when a goitre has already developed. The signs of thyrotoxicosis develop insidiously and are manifested by loss of body weight, irritability and palpitation. The ocular signs of thyrotoxicosis are very moderate in toxic adenoma and sometimes are even absent. A node of dense elastic consistency, with a smooth surface and clear boundaries is palpated in the tissue of one of the lobes of the thyroid gland. In distinction from a malignant tumour, adenoma of the thyroid is always easily mobile. Scanograms clearly demonstrate extremely high functional activity, size, and localization of the adenoma.

There is not a single constant sign in the clinical picture of thyrotoxicosis but the complex of the most common signs is so characteristic that the diagnosis of the syndrome is easily made in far-advanced cases. In atypical or less manifest cases the diagnosis must

always be confirmed by the results of laboratory tests and (which is much less conclusive) the favourable results of trial therapy with thyrostatic agents.

In the first half of the present century, thyroid function was determined by indirect methods among which measurement of the basal metabolic rate was given preference. Now the state of the thyroid gland is appraised by direct tests. The most valuable guiding tests are as follows: radioiodine uptake test, test for protein-bound iodine, and test for thyroxine content in blood serum. The last test is much more reliable in making the diagnosis because drugs do not affect its results.

Special methods of examination are applied when the clinical picture of the disease and the results of functional tests are in disagreement. Tests with tri-iodothyronine and the thyroid-stimulating hormone are the most widely used among them.

A disparity between the clinical findings and the results of laboratory tests is encountered particularly often in patients who had undergone thyroidectomy or who had been treated in the past with tri-iodothyronine or Mercazole (thiamazole). Despite the clinically manifest picture of thyrotoxicosis, iodine uptake by the thyroid gland, the content of protein-bound iodine and the concentration of total and free thyroxine in blood serum in these patients are often normal.

The increased content of tri-iodothyronine in plasma may be one of the causes of clinically manifest thyrotoxicosis. The blood tri-iodothyronine concentration in these patients is 6 to 8 times that of the normal value.

In some cases of euthyroid goitre, the concentration of protein-bound and free thyroxine in blood is unexpectedly below normal. It is assumed that normal thyroid function is maintained in such cases because the blood tri-iodothyronine content is above normal. A clinically euthyroid state in reduced blood thyroxine content is often encountered in patients who had been treated previously with radioiodine.

Tumours of the Thyroid Gland and Other Organs

Tumours of the thyroid gland. Enlargement of the thyroid gland with signs of thyrotoxicosis are found in patients with primary and metastatic tumours of the gland. Thyrotoxicosis usually develops only when the tumour is very large. This is explained by the fact that the tumorous tissue is functionally less active than the tissue

of the normal thyroid and that the function of the non-involved part of the gland is suppressed by the tumour.

Thyrotoxicosis in tumours of the thyroid has the same clinical picture as thyrotoxicosis in diffuse toxic goitre but the ocular signs described above are usually absent. Tumour of the gland should be cosidered in every case of thyrotoxicosis developing in a patient who had undergone thyroidectomy. Metastatic growths should be searched for especially persistently in patients who had been operated on for toxic adenoma of the thyroid gland or mixed (microfollicular) goitre. Experience shows that such growths may be detected before the gland is noticeably enlarged.

Hormonally active tumours of other organs. Dermoid cysts and teratoma of the ovaries containing hormonally active thyroid tissue are called *ovarian struma*. About 4 per cent of these tumours are attended by thyrotoxicosis. The true cause of the syndrome in such cases remains unrecognized for a long time. The thyroid gland is irregularly enlarged as a rule and a diagnosis of microfollicular (mixed) goitre is made. Subtotal resection of the thyroid is often carried out, but the signs of thyrotoxicosis either do not change in the postoperative period or subside only slightly. An euthyroid state occurs only after the ovarian tumour is removed.

A timely diagnosis of a hormonally active ovarian tumour is made only by performing simultaneous tests for the rate of radioiodine uptake both by the thyroid and the ovaries in a patient with thyrotoxicosis. Scanning of the ovaries after radioiodine prescription must be performed in every female with thyrotoxicosis and ovarian tumour. The presence of a hormonally active tumour should be suspected in all cases of Basedow's disease (exophthalmic goitre) when the signs of the disease do not disappear completely after subtotal thyroidectomy.

Thyrotoxicosis sometimes develops in patients suffering from *seminoma*, *chorionepithelioma*, and other tumours of trophoblastic origin. The clinical manifestations of the disease are usually mild. There is no exophthalmos as a rule. The thyroid is normal in size or somewhat enlarged but the basal metabolic rate and radioiodine uptake by the thyroid are increased in all cases. The content of protein-bound iodine in the plasma is noticeably above normal in all patients.

The development of thyrotoxicosis is explained by the intensification of thyroid function under the effect of factors produced by the tumour which resemble the pituitary thyroid-stimulating hormone in physiological action. Chemotherapy or surgical removal of the principal tumour leads to the disappearance of thyrotoxicosis. Chorionepithelioma should always be held in mind when signs of thyrotoxicosis occur in a female who is thought to be pregnant.

Thyrotoxicosis sometimes develops in *carcinoma of the bronchus*,

stomach or *pancreas*. Substances stimulating thyroid function are found in the blood of such patients. The radioimmunological method distinguishes them from the thyroid-stimulating hormone of the pituitary. Thyrotoxicosis in malignant tumours differs from the commonly encountered Basedow's disease. It occurs more often among males than among females, and mostly at elderly and old age. The thyroid in these patients is noticeably enlarged, but its enlargement is only attended by tachycardia. Exophthalmos does not develop.

Chromophobic pituitary adenoma (thyrotoxicosis caused by hypersecretion of the thyroid-stimulating hormone). The thyroid-stimulating hormone of the anterior pituitary lobe activates the function of the thyroid gland by increasing the rate of entry into the blood and the synthesis of its hormones. After hypophysectomy, the functional activity of the thyroid drops sharply and its parenchyma atrophies. Several cases of chromophobic tumour of the anterior pituitary attended by thyrotoxicosis have been described in the recent years.

The content of the thyroid-stimulating hormone in the blood of these patients is six to seven times the normal level. Increased radioiodine uptake by the gland and a high concentration of total and free thyroxine in the blood were found at the same time. After surgery and radiation therapy the content of the thyroid-stimulating hormone and the thyroid hormones in the blood reduced to normal levels, and the clinical manifestations of thyrotoxicosis disappeared completely.

The clinical picture of thyrotoxicosis associated with hypersecretion of the thyroid-stimulating hormone has no specific signs. Increased secretion of the thyroid hormones is the underlying factor. The true cause of thyrotoxicosis in patients with chromophobic tumour of the anterior pituitary was suspected because visual disorders and other signs of cerebral tumour appeared and was confirmed by testing the concentration of the thyroid-stimulating hormone in the blood.

Thyrotoxicosis Caused by Iodine or Thyroid Preparations

Small doses of iodine and its preparations are used widely in the prevention of goitre and in the treatment of thyrotoxicosis. That prolonged medication with iodine even in small doses may cause the development of thyrotoxicosis is also a well-known fact of long standing. It was reported that the iodination of bread in regions of endemic goitre leads to an increase in the number of cases with thyrotoxicosis.

Long-term treatment of patients suffering from non-toxic goitre with iodine also often induces thyrotoxicosis. Why the effect of iodine on thyroid function is favourable in some cases and undesirable in others is not clear to date. Stout women sometimes take thyroid preparations to reduce their body weight. The degree of manifestation of hyperthyroidism in such cases is determined by the dose and biological activity of the preparation.

Artificially induced thyroid hyperfunction is attended by increased basal metabolic rate. The blood thyroxine content grows in a patient given the drug. The possibility that thyrotoxicosis is caused by medication with preparations of iodine or the thyroid gland should be considered in patients who have an increased content of thyroxine in the blood and an increased basal metabolic rate. Radioiodine uptake by the thyroid gland is diminished in these patients. The normal relationship between the clinical findings and the results of laboratory tests is restored only several months after the drug is discontinued.

Thyroiditis

Enlargement of the thyroid with thyrotoxicosis, usually mild, is sometimes encountered in subacute (granulomatous) and chronic (autoimmune) thyroiditis.

de Quervain's subacute thyroiditis is probably of virus origin. It sets in with fever, pronounced indisposition, and headache. Diffuse or focal enlargement of the thyroid and its marked tenderness with the pain referred to the ears and back of the head are characteristic signs. The gland is not fused with the adjacent tissues and moves during swallowing. The disease takes an undulant course and in most cases does not develop into myxoedema. Tenderness produced on palpation of the gland is the principal diagnostic sign of subacute granulomatous thyroiditis marked by thyrotoxicosis.

The uptake of radioiodine by the thyroid is noticeably reduced in subacute thyroiditis. The content of thyroxine (and, consequently, of protein-bound iodine) in blood serum is increased. Antithyroid antibodies are detected in almost every patient, but always in low titres.

Chronic lymphocytic thyroiditis (Hashimoto's disease) usually begins insidiously with enlargement of the thyroid gland. Antibodies in high titres are found in the blood plasma of most patients. Just as in other autoimmune diseases, the content of gamma globulins in the blood plasma is increased in most cases of chronic thyroiditis. Like in Basedow's disease, ophthalmopathy and pretibial oedema may be encountered. Signs of thyrotoxicosis rarely occur in the initial stages of Hashimoto's disease and are usually moderate.

Basal metabolic rate is increased. The disease is characterized by a high content of protein-bound iodine and increased uptake of radioiodine by the thyroid gland. An inflammatory process that tends to advance for a lengthy period of time terminates in the development of myxoedema. The diagnosis of Hashimoto's disease is indirectly confirmed by marked improvement in the patient's condition (with diminution in the size of the goitre and alleviation of thyrotoxicosis) under the effect of treatment with steroid hormones. The diagnosis of chronic thyroiditis must be confirmed in all cases by the results of the precipitation reaction or the findings of needle or operative biopsy of the thyroid gland.

Chronic thyroiditis often has to be differentiated from carcinoma of the thyroid, which also may be attended by thyrotoxicosis. In considering this problem it must be borne in mind that Hashimoto's disease is marked by diffuse enlargement of the thyroid whereas carcinoma always begins with involvement of only one of its lobes. This difference is most easily detected by scanning of the gland. A radioiodine 'accumulation defect' is seen where the tumour is localized.

Trial therapy with steroid hormones is always unsuccessful in carcinoma of the thyroid, but often causes a diminution in the size of the gland and an improvement in the condition of a patient with Hashimoto's disease. Both diseases may occur simultaneously in a patient and the final diagnosis may therefore be established only from the results of operative biopsy.

Supplement XII-1

Causes of Thyrotoxicosis

1. Toxic goitre.
   - Diffuse.
   - Nodular.
   - Mixed.
   - Tri-iodothyronine-induced.
2. Tumour of the thyroid gland and other organs.
   - Thyroid carcinoma.
   - Toxic adenoma.
   - Ovarian struma.
   - Seminoma.
   - Chorionepithelioma.
   - Carcinoma of the bronchus, stomach, pancreas or prostate gland.
   - Chromophobic pituitary adenoma.
3. Medication with iodine or thyroid preparations.
4. Thyroiditis.
   - Subacute (de Quervain's).
   - Chronic (Hashimoto's disease).

Chapter XIII

Haemoptysis and Pulmonary Haemorrhage

The expectoration of blood is called haemoptysis. It is usually encountered in bronchial carcinoma or pulmonary tuberculosis. In most cases blood is expectorated from the respiratory tract together with sputum; in copious pulmonary bleeding the expectoration and swallowing of blood occur simultaneously. Vomiting sometimes occurs during a severe cough and the swallowed blood is discharged from the stomach and simulates bloody vomit. The opposite is also encountered. In copious bleeding from the stomach and subsequent bloody vomiting, the mouth and nose are filled with blood some of which is aspired and then expectorated, simulating haemoptysis.

Table 2 shows the main signs which help in distinguishing haemoptysis from bloody vomiting. Proper differential diagnosis depends not only on the presence or absence of these signs but on the

Table 2

Signs Distinguishing Haemoptysis from Bloody Vomiting

Haemoptysis	Bloody vomiting
1. Blood is expectorated	Blood is discharged during vomiting
2. Blood is scarlet and has an alkaline reaction	Blood is often dark red, sometimes brown, has an acid reaction
3. Some of the expectorated blood is frothy	No frothy blood is discharged
4. After copious haemoptysis small amounts of sputum with an admixture of blood are expectorated for several days	Sputum is not expectorated after haemorrhage
5. The patient has a history of pulmonary diseases. Tickling or gurgling is felt in the throat shortly before haemoptysis begins	The patient has a history of liver or stomach diseases with the dyspeptic or pain syndromes. Bloody vomiting is often preceded by syncope
6. Melaena rarely appears after haemoptysis	Melaena is encountered very often after bloody vomiting
7. Haemoptysis usually continues several hours and sometimes even several days	Bloody vomiting is brief as a rule and copious

physician's skill in distinguishing their nuances and comparing the detected signs with the results of other methods of examination.

As in any case, the medical history is the background against which the disease weaves its pattern by means of the signs. A correct appraisal of this background always makes it easier to interpret at times extremely complicated pattern composed by the symptoms and signs of the disease. When talking with the patient or his relatives it is necessary to ask them in detail about the time of the blood expectoration, whether blood was expectorated with or without a cough, about the appearance of the blood, whether the haemoptysis had occurred before and how often, how much blood had been discharged during the given (last) haemoptysis and how much during the previous haemorrhages. If the physician had witnessed the haemorrhage himself he will distinguish haemoptysis from blood vomiting without much difficulty, but it will be a great problem if the conclusion has to be based on the patient's narrative.

The discharge of bright red blood is not an absolute sign of haemoptysis. Such blood is sometimes encountered in bloody vomiting, particularly in arterial gastric haemorrhage and in bleeding from dilated oesophageal veins. The usual venous blood is discharged in the last case and its haemoglobin is rapidly oxidized when it comes in contact with the oxygen in the air. Blood discharged in infarction is often dark red. On contact with the air it turns scarlet because it contains no haematin hydrochloride. Frothy blood is never found in bloody vomiting but is often encountered in haemoptysis.

An admixture of food particles is a frequent finding on gastric haemorrhage, but may be encountered in haemoptysis too if the expectorated blood was swallowed and then discharged with the vomit. A tarry stool appears after every more or less copious gastro-intestinal bleeding. It may also be passed after haemoptysis if much of the expectorated blood had been swallowed. It should be borne in mind that this complication is extremely rare in haemoptysis, especially if blood is expectorated from the lungs. A tarry stool appears at times after bleeding from the upper respiratory tract.

All the differential-diagnostic signs listed in Table 2 may be insufficiently pronounced in copious haemorrhages. Both in haemoptysis and in bloody vomiting the blood may be bright red with no admixtures of sputum or gastro-intestinal contents. The differential diagnosis of the bleeding in such cases is made from the results of objective examination of the patient with due consideration for the peculiarities of the course taken by the diseases that are compared. Aspiration pneumonia often develops after haemoptysis or moist rales are heard on the side of the affection. No pulmonary abnormalities are found after bloody vomiting as a rule. Diseases of the lungs

or heart are often disclosed in a patient with haemoptysis, diseases of the gastro-intestinal tract or portal hypertension are found in one with bloody vomiting. In Yablokov's (1944) experience, copious haemoptysis is usually encountered only in extensive destructive affections of the lungs which are easily disclosed by physical and X-ray examination of the patient. If after routine methods of examination the cause of haemoptysis is still not clear, systematic search for the cause of the bleeding must be begun. Supplement XIII-1 may be of some help in this search.

The blood that has escaped is partly expectorated, or partly resorbs and partly stays in the bronchi narrowing them or even causing their total obstruction. Atelectases occur, with the infection of which pneumonia develops. Body temperature is usually elevated on the second or third day after the bleeding. The fever is caused by resorption of blood from the bronchial tree and concomitant infection. The severity of the fever is determined by the body reactivity and the spread and virulence of the infection. Body temperature is high in some cases and subfebrile in others. A febrile reaction may be absolutely absent in old patients. The blood abnormality is leucocytosis, the leucocyte count varying noticeably from one case to another.

Aspiration pneumonia usually occurs on the second or third day after the haemorrhage. In protracted and not very copious bleeding it may develop later. Blood retained in the bronchi gradually moves into the lowest parts of the lung because of its weight; moist non-consonant rales reveal its presence there. When atelectases and pneumonia develop, the rales become consonant and respiration is either diminished or bronchial. X-ray demonstrates localized shadows usually in the inferior pulmonary lobe. These shadows are round in some instances or have all the signs of atelectases in others. Their size is determined by the volume of aspirated blood. Massive atelectases may develop in copious haemorrhages in which case the mediastinal organs are displaced to the side of the affection.

Pneumonia developing after bleeding is sometimes microfocal and extensive. It can hardly be distinguished from haemogenic disseminated pulmonary tuberculosis by X-ray. Rapid disappearance of the localized shadows without any traces leaves no doubt that their occurrence can be attributed to the development of microfocal atelectases. In distinction from the shadows in pneumonia, these microfocal shadows may develop both in the affected side and in the contralateral lung. Their development is associated with the aspiration of blood from the trachea into the bronchioles of the intact lung.

Haemorrhage from the Upper Respiratory Tract

Blood is sometimes expectorated in haemorrhage from the upper respiratory tract. In nasal haemorrhages blood may flow out through the nose and may flow back into the nasopharynx from which it is expectorated with the mucus. In sufficiently copious bleeding from the nose or nasopharynx, some of the blood is coughed out and some swallowed. Accumulation of blood in the stomach may induce bloody vomiting. The clinical picture becomes more complicated.

Haemorrhage from the upper respiratory tract occurs in alveolar pyorrhoea and diseases of the nasopharynx, gums, larynx, and the root of the tongue. Most of these patients apply immediately to physicians specializing in the respective field and only patients with bleeding from telangiectases remain under the care of internists for a long time. Study of the medical history of the patient's relatives and the detection of multiple telangiectases on the mucous membrane of the lips, mouth, nose, pharynx and larynx help greatly in most cases in establishing the diagnosis of this hereditary disease. Telangiectases may form on the mucous membrane of the trachea, bronchi, and other organs. Recurrent haemorrhages are the main sign of the disease. The diagnosis is considered proved only when all other sources of the bleeding are ruled out.

Small amounts of blood with sputum are often expectorated in chronic diseases of the nasopharynx and gums. In the mornings such patients cough up a few spits of mucopurulent sputum with an admixture of blood in the form of clots or a fine honeycomb network on its surface. Some authors call such bleeding 'false haemoptysis' striving to distinguish it from true and often life endangering haemoptysis in haemorrhage from the bronchi and lungs.

Haemorrhage from the Trachea and Bronchi

Bronchitis and bronchiectasis. Acute and chronic diseases of the bronchi may lead to haemoptysis. Blood enters the bronchi from small vessels of the mucous membrane during forceful cough. It is found on the surface of the sputum in bright red streaks or is mixed with the sputum into a homogeneous reddish-grey mass. This latter type of sputum is encountered in fibrinous (pseudomembranous) bronchitis. Haemoptysis may be considered associated with

acute bronchitis or exacerbation of chronic bronchitis when tuberculosis of the lungs and tumour of the bronchus are ruled out.

Haemoptysis is often caused by bronchiectasis. Recurrent haemoptysis may be the only clinical manifestation of 'dry bronchiectasis' the diagnosis of which may be established convincingly only after bronchography. About 50 per cent of cases of bronchiectasis marked by the expectoration of a considerable amount of sputum are also complicated by haemoptysis which usually occurs during exacerbations of the inflammatory process. Perifocal pneumonia developing in such cases may be marked by a protracted period of subfebrile temperature as a result of which a symptom complex resembling that in pulmonary tuberculosis occurs.

The differential diagnosis between these diseases is based on information gained from the medical history, repeated search for *Mycobacterium tuberculosis* in the sputum, and repeated X-ray examination. The findings of physical examination may also be of some help. Bronchiectases are usually encountered in patients who have other signs of pulmonary fibrosis which is usually consequent upon pneumonia or pulmonary suppuration suffered earlier. Bronchiectases are mostly found in the lower parts of the lungs, often in combination with coarse distortion of the pulmonary pattern. Bronchography demonstrates the bronchiectases, of course, but does not rule out simultaneous affection with tuberculosis of the lungs.

Haemorrhages in bronchiectasis are mild as a rule and recur. Bleeding that endangers the patient's life is very rare. The common source of the haemorrhages are arteriovenous anastomoses in the walls of large bronchi which can be inspected by means of modern bronchoscopes. Bronchiectases are so often complicated by bleeding that they should be presumed whenever recurrent haemoptysis occurs in a patient who has no signs of pulmonary tuberculosis.

Tumours of the bronchi. Haemoptysis is an early sign of central or peripheral pulmonary carcinoma. This diagnosis is most probable if haemoptysis appears for the first time at an elderly age. Unfortunately, this sign is encountered by far not in every case of the disease. Clinicians practicing in the past believed that in carcinoma of the lung sputum had the characteristic appearance of raspberry or black currant jelly. Today it is not accepted as a pathognomonic sign. Sputum which looks like raspberry jelly may be discharged in many other diseases, tuberculosis, actinomycosis, bronchiectasis, and pulmonary infarction among others. Haemoptysis in carcinoma of the lung is often persistent. It may continue for several weeks and even months. Haemoptysis of approximately such duration is sometimes encountered in other diseases too, e.g. in bronchiectasis and pulmonary tuberculosis. Every case of haemoptysis in persons over the age of 40 should be regarded as an indica-

tion for clinical and X-ray examination of the lungs in which particular attention is focused on the detection of carcinoma of the lung. At the current level of knowledge, X-ray examination with the use of bronchography and tomography is of decisive significance in the early diagnosis of pulmonary carcinoma. Atelectasis of a pulmonary lobe or segment develops in rather late stages of the disease. Ventilation disorders are the earliest X-ray signs of central pulmonary carcinoma. This type of carcinoma usually resembles pneumonia in the clinical manifestations. Much less frequently it is mistaken for tuberculosis of the lungs. The diagnosis of carcinoma of the lung can be made much earlier if examination by tomo- and bronchography of all patients with pneumonia which does not resolve within two or three weeks (see 'Unresolved Pneumonia') is made a rule.

It is more difficult to make the diagnosis of peripheral carcinoma of the lung; it is often mistaken for an area of pulmonary fibrosis. If the suspicious shadowed area is produced by a tumour of the lung, tomograms will demonstrate the characteristic signs of a new growth, namely, irregular outlines and multinodular pattern of the shadow. These structural details of a tumour are not found on the usual radiographs.

Recurrent haemoptysis may also be induced by benign tumours of the bronchi, e.g. adenoma. The new growth is predominantly found among females. Adenomas are usually localized in the main bronchi and are therefore detected relatively easily by bronchoscopy or bronchography. Clinical and X-ray examination often cannot reveal this tumour.

Diseases of the Lungs

Pulmonary tuberculosis. Haemoptysis may occur in any stage of pulmonary tuberculosis but is encountered most frequently in the fibrocavitary form and in patients with tuberculous cirrhosis. Pulmonary haemorrhage and haemoptysis are encountered in 30 to 50 per cent of cases with fibrocavitary tuberculosis of the lungs, moreover, in 8 to 12 per cent they are fatal (Knyazhetsky, 1972). These forms of tuberculosis are not a diagnostic problem. Most patients have a long history of pulmonary tuberculosis and physical and X-ray examination provides evidence of foci of fibrosis and cavities in the pulmonary tissue. *Mycobacterium tuberculosis* and elastic fibres are often found in the sputum.

Haemoptysis may be an early clinical sign of tuberculosis of the lungs. It occurs occasionally in patients with a primary complex. In tuberculosis of the bronchial nodes the caseous material may rupture into the bronchi or into the trachea with simultaneous ulcera-

tion of the wall of more or less large vessels. The physical signs of tuberculosis may be absent or hardly manifest. X-ray examination discloses infiltration and sometimes disintegration of the pulmonary tissue. If expectorated, the sputum must be examined for *Mycobacterium tuberculosis* by direct bacterioscopy and by the flotation method, luminescent microscopy and culture. If the sputum is not expectorated, laryngeal scrapings and gastric waters are examined.

According to some authors, haemoptysis is encountered in 9-15 per cent of cases with focal pulmonary tuberculosis. Thermoregulation disorders, when physical signs of the disease are insufficient, are a characteristic feature of this form. Such patients are often kept under long-term surveillance by physicians of out-patient clinics for protracted subfebrile temperature of unknown aetiology, influenza-like diseases and other manifestations which are actually caused by active focal tuberculosis. The process is usually localized in the apex of the lungs over which shortening of the percussion sound, coarse respiration and moist, fine bubbling rales are sometimes determined. In the phase of disintegration the rales become more constant. Despite the negligible clinical data, recurrent, usually small haemoptyses are often encountered. Copious bleeding is very rare in this form of tuberculosis.

Other pulmonary diseases. Haemoptysis is almost a constant sign of lobar *pleuropneumonia*. The sputum has a characteristic rusty appearance in most cases. Marked bleeding is sometimes encountered in influenzal pneumonia and in pneumonia caused by *Bacillus friedländeri* or staphylococcus. Copious bleeding is usually evidence of particularly severe pneumonia.

Haemoptysis occurs in approximately 50 per cent of cases of *pulmonary suppuration*. The bleeding is explained by involvement in the destructive process of vessels in the purulent focus. Sputum with an admixture of blood is coughed up in large amounts in most cases. Profuse bleeding is much less frequent. It occurs from vessels in which thrombi had no time to form during melting of the pulmonary tissue. Bleeding in embolic pulmonary abscesses is a particularly frequent occurrence (in 85-88 per cent of cases). Pulmonary suppuration may be combined with tuberculosis of the lungs. The diagnosis in such cases may be reliably verified by the characteristic X-ray signs of pulmonary tuberculosis. The results of repeated examination of the sputum for *Mycobacterium tuberculosis* may greatly help in identifying the true cause of the malady.

Parasitic diseases of the lungs are sometimes manifested by allergic reactions (e.g. Loeffler's syndrome) and at times by focal lesions resulting from the direct effect of the causative agent on the lung. In this instance destruction of the pulmonary tissue may occur and lead to haemoptysis or even copious pulmonary bleeding.

Haemoptysis in *hydatid disease of the lungs* may be the first sign compelling the patient to apply for medical aid. A small admixture of blood in the sputum is found in some cases of the disease, spitting of pure blood in others and severe bleeding in still others. At the onset of the disease haemoptysis may be associated with rupture of the vessels of the cystic capsule during cough. Rupture of the hydatic cyst is sometimes attended by copious pulmonary haemorrhage.

Ascaris larvae migrate through the lungs and cause the formation of short-lived focal infiltrates with a diameter of up to several centimetres. This period of ascariasis is clinically manifested by cough, retrosternal pain and, in graver cases, by haemoptysis and dyspnoea. Dry and moist rales are sometimes auscultated. Leucocytosis is found in the blood, sometimes as high as 20 000, with high eosinophilia. The eosinophil content sometimes reaches 30-70 per cent. Body temperature is usually subfebrile. The diagnosis is verified by the discovery of *Ascaris* larvae in the sputum or the gastric contents. The discharge of adult worms from the intestine or the discovery of their eggs in the faeces may be indirect confirmation of the diagnosis.

Paragonimiasis is a very common disease. In the Soviet Union it is encountered in the Far East. Crabs, crayfish or water contaminated by them are the source of the infection. In man the lungs are a constant habitat for the parasite. The disease takes a relatively mild course with the formation of pulmonary granulomas after the disintegration of which thin-walled cysts 0.5 to 5.0 cm in diameter form. Haemoptysis, usually small, occurs almost in every case of paragonimiasis. It may continue for several years. Shortness of breath, subfebrile temperature, anorexia and loss of body weight develop simultaneously with haemoptysis. Neither leucocytosis nor eosinophilia is usually encountered. In rare cases the disease is complicated by pleurisy or diarrhoea. Moderate anaemia is often found. The diagnosis is established when the ova of *Paragonimus westermani* are discovered in the sputum and stool. To identify them, the preparations simply must be stained by Papanicolaou's stain.

Strongyloidiasis (Cochin-China diarrhoea) is widely prevalent in countries with a hot and humid climate, but is also encountered in countries with a moderate climate. It is rare in the Soviet Union. Mild and moderately severe cases are marked by abdominal pain and diarrhoea. Severe invasion is attended by bronchospasms, dyspnoea and sometimes also by haemoptysis. The diagnosis is established when larvae of *Strongyloides stercoralis* are found in the sputum and stool.

Haemoptysis and pulmonary haemorrhages in injuries to the thoracic cavity and in some occupational diseases (pneumoconiosis, silicosis, berylliosis, etc.) are commonly known and their diagnosis is obvious even before complications set in.

Diseases of the Cardiovascular System

Haemoptysis is a common phenomenon in diseases of the cardiovascular system. It is particularly frequently encountered in *mitral stenosis* and other heart diseases combined with left-ventricular failure and pulmonary hypertension. Moderate or insignificant haemoptysis, often recurrent, may be observed in mitral stenosis before right-ventricular failure develops. There is no difficulty in identifying the cause of haemoptysis in such cases.

Haemoptysis is also among the most frequent signs of *pulmonary infarction*. In typical cases the disease begins with paroxysmal dyspnoea which is followed by haemoptysis, pain in the side, and a more or less lengthy period of fever. Severe dyspnoea which sometimes develops into paroxysmal dyspnoea is among the constant signs of left-ventricular failure, consequently the formation of an infarct in the lungs in left-ventricular failure is usually disclosed only after chest pain and haemoptysis appear. Physical examination of a patient with more or less extensive infarct often reveals a dulled percussion sound and pleural friction rub. The appearance of fine bubbling rales indicates that peri-infarction pneumonia has developed. Accumulation of haemorrhagic effusion is sometimes discovered in the pleural cavity in extensive infarcts.

Pulmonary infarction often develops in patients prescribed long-term bedrest. These are patients with heart failure, cerebral haemorrhages, bone fractures, and all patients who had undergone serious surgical operations. The direct cause of the infarction in most cases are phlebothromboses which occur particularly often in the true pelvis and in the lower limbs. A sudden deterioration in the condition of these patients is usually caused either by pneumonia or by pulmonary infarction. In considering the differential diagnosis between these two clinical syndromes attention should be specially focused at the sequence in which these practically the same signs appear.

A chill at the very onset of the disease and sudden deterioration in the patient's condition are encountered only in pneumonia. Paroxysmal dyspnoea is of little differential diagnostic significance, because it may develop at the beginning of both pneumonia and pulmonary infarction. Pain in the side and fever are the first manifestations of pneumonia in most cases. Sputum with an admixture of blood is expectorated later.

In pulmonary infarction fever appears later than haemoptysis. Great differential diagnostic significance should also be attached to leucocytosis which is found on the first day of pneumonia, but

grows gradually in pulmonary infarct. Haemorrhagic effusion in the pleural cavity is characteristic of infarction in the lungs. Pneumonia is complicated by purulent pleurisy, the clinical picture of which differs sharply from that of reactive pleurisy in pulmonary infarction. The results of X-ray examination are of great help in the differential diagnosis of these two syndromes. The characteristic, clearly outlined triangular shadow of the infarct is in most cases easily distinguished from the pneumonic infiltrate lacking distinct boundaries.

Pulmonary haemorrhage may be a consequence of rupture of *aneurysm of the aorta* into a bronchus or into the pulmonary parenchyma. This happens in syphilitic aneurysm of the aorta and in its dissecting aneurysm. Rupture of the aneurysm into a bronchus results in fatal haemorrhage from the mouth. In all cases of rupture of a dissecting aortic aneurysm into the lung we observed entry of blood into the left pleural cavity simultaneously with haemoptysis. The pain syndrome at the peak of which haemoptysis appears predominates in the clinical picture of the disease.

Supplement XIII-1

Causes of Haemoptysis and Pulmonary Haemorrhage

1. Diseases of the upper respiratory tract.
   - Alveolar pyorrhoea.
   - Telangiectasia.
2. Diseases of the trachea and bronchi.
   - Bronchitis.
   - Bronchiectasia.
   - Bronchial tumour.
     - Benign.
     - Malignant.
3. Diseases of the lungs.
   - Pulmonary tuberculosis.
   - Pneumonia.
   - Pulmonary suppuration.
   - Parasitic diseases of the lungs.
   - Hydatid disease of the lungs.
   - Ascariasis.
   - Paragonimiasis.
   - Strongyloidiasis.
   - Occupational pulmonary diseases.
4. Diseases of the cardiovascular system.
   - Mitral stenosis.
   - Pulmonary infarction.
   - Aneurysm of the aorta.

Chapter XIV

Heart Failure

The diagnostic reasoning at the bedside of a patient with chronic heart failure should begin by clarifying the *sequence in the appearance* of its most easily detected symptoms: oedema, dyspnoea, paroxysmal dyspnoea and hepatomegaly. It is best to evaluate the collected facts according to the scheme shown in Supplement XIV-1 which envisages the recognition of three types of heart failure, namely, right-ventricular, biventricular and left-ventricular. Each of these types is induced only by a few diseases, which makes the main diagnostic problem, the establishment of the only cause of its development, easier.

Heart failure in ischaemic heart disease and valvular heart diseases begins as a rule with dyspnoea developing on physical effort. Nocturnal paroxysmal dyspnoea, enlargement of the liver and oedema develop soon in attendance. Heart failure becomes biventricular.

Isolated right-ventricular failure is a rare occurrence. It begins with enlargement of the liver and oedema. In most cases it is caused by diseases of the pulmonary parenchyma, pulmonary vessels, and chest, and alveolar hypoventilation, in others by tumours and some congenital diseases. Diffuse heart diseases usually set in with a picture of biventricular circulatory insufficiency with approximately simultaneous development of the symptoms and signs of left-ventricular and right-ventricular failure.

Right-ventricular Failure

Congenital pulmonary valvular insufficiency. Congenital pulmonary insufficiency resulting from deficient development, fusion or fenestration of the valve cusps is among the rare causes of right-ventricular failure. Isolated congenital pulmonary insufficiency was diagnosed during life for the first time in 1955 in a 24-year-old medical student. He had asymptomatic congenital pulmonary valvular insufficiency but no complaints.

Pulmonary insufficiency cannot be referred to harmless developmental anomalies. Some carriers of this anomaly develop signs of failure of the right ventricle after several decades of normal life, and the advancement of these signs leads to an unfavourable out-

come. In the available literature, we found detailed information on four proved cases of isolated insufficiency of the pulmonary valve. One female patient died at the age of 64 from heart failure; a bicuspid valve of the pulmonary artery was found on autopsy. Heart failure in the other three patients developed at the ages of 21, 34 and 54. Insufficiency of a quadricuspid valve of the pulmonary artery was recognized as its only cause.

Valvular disease in itself is only one of the causes of right-ventricular failure. It remains compensated till pulmonary hypertension develops under the effect of which more blood is regurgitated in the right ventricle and mild pulmonary valvular insufficiency gradually becomes severe. The work load of the right ventricle increases because, in addition to overload by pressure, it experiences the increasing overload by the blood volume.

Congenital pulmonary valvular insufficiency is usually discovered by accident during examination of healthy individuals. A diastolic murmur and dilatation of the pulmonary artery are its main diagnostic signs. The diastolic murmur is best heard close to the sternum in the second and third left intercostal spaces. It can be seen on the phonocardiogram that it is spindle-shaped and occupies only the middle of diastole. The first heart sound is normal, the second sound is diminished and consists of only the aortic component. In addition to the diastolic, a systolic murmur is often heard, which is diamond-shaped and occupies the middle of systole. Increased systolic ejection into the pulmonary artery leads to the origin of the systolic murmur and, in more severe cases, to intensified pulsation of the pulmonary artery in the second intercostal space at the sternum.

In mild pulmonary valvular insufficiency the ECG is normal; in instances of marked regurgitation it shows signs of increased work load of the right ventricle.

X-ray makes it possible to reveal one of the main signs of congenital pulmonary valvular insufficiency, dilation of the pulmonary trunk and the right and left pulmonary arteries. The peripheral vessels of the lungs are normal in appearance.

Congenital pulmonary valvular insufficiency in clinical manifestations most closely resembles relative pulmonary insufficiency developing as a complication of pulmonary hypertension and congenital dilatation of the pulmonary artery.

Pulmonary hypertension (primary or secondary) of a sufficient length of time and degree of manifestation leads to distension of the valvular ring of the pulmonary artery and relative pulmonary insufficiency develops. A diastolic murmur is one of its main diagnostic signs. It begins immediately after the pulmonary second sound and occupies entire, or almost entire diastole. Its intensity is maximum at the beginning of diastole, but diminishes noticeably by

the middle of diastole. At the end of diastole the murmur ceases. As it is pointed out above, the murmur in congenital pulmonary valvular insufficiency occupies only the middle of diastole. The pulmonary second sound is diminished in congenital pulmonary valvular insufficiency but heard clearly or intensified in pulmonary hypertension with relative pulmonary insufficiency.

Dilatation of the pulmonary artery in pulmonary hypertension contrasts with the poor vascular pattern on the periphery of the lung. When pulmonary hypertension leads to the development of relative pulmonary insufficiency the vascular pattern on the lung periphery is often not seen at all. In congenital pulmonary valvular insufficiency the vascular pattern on the periphery of the lungs does not change.

The diastolic murmur is heard in congenital pulmonary valvular insufficiency irrespective of the signs of heart failure, but in pulmonary hypertension it usually appears together with heart failure. Successful treatment is attended by diminution or disappearance of the diastolic murmur of relative pulmonary insufficiency, but has no effect on its intensity in congenital insufficiency of the pulmonary valve.

The presence of the symptoms of the principal disease which had caused the development of pulmonary hypertension and relative pulmonary insufficiency also makes the differential diagnosis easier. Congenital pulmonary valvular insufficiency may be erroneously diagnosed as *congenital dilatation of the pulmonary artery* in which a diastolic murmur is sometimes heard. It is fairly easy to differentiate these diseases because pulmonary valvular insufficiency is always attended by hypertrophy of the right ventricle and is sometimes complicated by heart failure. Right-ventricular hypertrophy is never encountered in congenital dilatation of the pulmonary artery. Regurgitation of blood into the right ventricle is negligible in this disease and never leads to the development of right-ventricular failure.

Right-ventricular failure may be caused by **pulmonary stenosis.** Infundibular and subinfundibular stenoses of the pulmonary artery are always combined with ventricular septal defect. Heart failure in these variants of pulmonary stenosis is marked by temporary or permanent cyanosis. Valvular and supravalvular stenoses are often encountered as isolated lesions; the latter variant of the stenosis is among exceptionally rare diseases. Patients with these variants of pulmonary stenosis are not cyanotic.

Isolated valvular stenosis of the pulmonary artery may follow an asymptomatic course for a long time. Depending on the severity of the stenosis, the first complaints appear between the ages of 10 and 40. Dyspnoea on physical effort and increased fatiguability are

the earliest symptoms. Right-ventricular failure occurs suddenly as a rule, and takes an irresistably progressive course. The clinical picture of right-ventricular failure comprises signs typical of pulmonary stenosis and tricuspid insufficiency. Patients with mild or moderate stenosis usually come under the observation of an internist. The carriers of this anomaly sometimes live to the age of 70.

Compensation in pulmonary stenosis is achieved at the expense of hypertrophy of the right ventricle whose intensified pulsation may be determined in the third intercostal space at the left sternal border. The first heart sound remains normal in valvular stenosis. It is attended by a high-frequency ejection sound which is best heard in the second left intercostal space. The severer the stenosis, the shorter is the time interval between the first sound and the ejection sound. In mild stenosis both sounds are separated by an interval which is perceived by ear. In very severe stenosis the ejection sound disappears and only the first sound remains. A symmetric diamond murmur in severe stenosis persists till the aortic component of the second sound or even beyond it, muffling this component. Maximum intensity of the murmur in such cases shifts to the second half of systole.

Right-ventricular failure in pulmonary stenosis is distinguished from that in rheumatic heart disease and cardiosclerosis by the character of the pulmonary vascular pattern. Gradual dilatation of the pulmonary trunk is the characteristic sign of valvular pulmonary stenosis. The extent of this dilatation correlates well with the severity of the stenosis. The left pulmonary artery is particularly sharply dilated. Aneurysm of this artery sometimes develops. The walls of the aneurysm may calcify. Marked dilatation of the pulmonary artery in pulmonary stenosis is accompanied by a normal or even an impoverished vascular pattern of the lungs.

In mild stenosis the ECG is normal. In graver cases signs of right-atrial and right-ventricular hypertrophy are always present. The degree of these signs is in good correlation with the severity of the stenosis. The height of *P* wave in the first thoracic lead reflects adequately the blood pressure level in the right ventricle of the heart.

The final diagnosis of pulmonary stenosis is established from the results of catheterization of the right heart cavities. Pulmonary stenosis is marked by increased blood pressure in the right ventricle and low systolic pressure in the pulmonary artery. The same method is applied in revealing infundibular stenosis of the pulmonary artery.

Supravalvular stenosis of the pulmonary artery is a non-progressive congenital heart disease. Its severity does not grow with age. Heart failure usually does not develop in such patients.

Heart failure in pulmonary stenosis is distinguished by an un-

favourable course. Therapeutic measures usually bring about only a brief improvement in the patient's condition. Death occurs in one or two years after the appearance of oedema. Right-ventricular failure in pulmonary stenosis is marked by isolated development. It is never attended by signs of left-ventricular failure. The characteristic X-ray picture of pulmonary stenosis is never encountered in any other disease.

Right-ventricular failure is an essential syndrome of **Ebstein's anomaly** which is marked by malformation of the tricuspid valve usually with a patent foramen ovale or atrial septal defect. The cusps of the valve are distorted and displaced in the direction of the apex of the right ventricle. The papillary muscles are deficiently developed, deformed and shortened. The fibrous ring is always dilated. The parts of the left heart are normal. The aorta and pulmonary artery are hypoplastic.

Approximately 20 per cent of patients have neither an atrial septal defect nor cyanosis, and may lead a normal life and even be engaged in heavy manual labour for many years. As a rule, patients die from right-ventricular failure four to twenty years after its appearance. Death may strike suddenly with no obvious cause. Patients with Ebstein's anomaly tend to develop paroxysmal arrhythmias. If a patient with this disease has an atrial septal defect, cyanosis usually makes an appearance for the first time during an attack of cardiac fibrillation or paroxysmal tachycardia.

Thicuspid insufficiency is an obligatory sign of Ebstein's anomaly. It would seem that a positive venous pulse is determined in every case of this disease, but the pulse in the jugular vein may be normal. Systolic pulsation of the enlarged right ventricle in rheumatic heart diseases is best detected at the sternal margin in the fourth intercostal space; there is no systolic pulsation of the right ventricle in Ebstein's anomaly. Pulsation of the outflow tract of the right ventricle, which is projected in the third intercostal space, is usually found in these patients. In all cases of the disease there is a dull percussion sound to the right of the sternum caused by enlargement of the right atrium.

Ebstein's anomaly differs from other diseases of the tricuspid valve also in the results of heart auscultation. The systolic murmur of tricuspid insufficiency is heard almost in all cases of Ebstein's anomaly. This harsh scraping murmur usually occupies whole (or almost whole) systole. Its maximum is situated between the sternum and the apex of the heart. Although this is a tricuspid murmur, it is not intensified during inspiration because the weak right ventricle cannot augment its systole during intake of breath.

The first heart sound in Ebstein's anomaly is often split because of the almost constantly encountered right bundle branch block. The combination of these disorders leads to the third or fourth heart

sound being audible in all cases of Ebstein's anomaly. The summation of the third and fourth heart sounds may create the impression of a diastolic murmur. The phonocardiogram at times records a presystolic murmur probably caused by functional stenosis of the right venous orifice.

Right bundle branch block is found in approximately 95 per cent of cases of this disease and is in many instances combined with delayed atrioventricular conduction. No less significant diagnostic importance is attached to changes in *P* wave. Zubarev (1975) found high *P* wave in 70 per cent of cases with Ebstein's anomaly which he examined. It was demonstrated particularly clearly in leads I, II and V_1. In an asymptomatic course of the disease the atrial waves may be normal.

In severe cases of Ebstein's anomaly the dimensions of the heart become sharply increased because the right atrium and right ventricle are enlarged. The right boundary of the heart is formed by the distended right atrium and the atrial part of the right ventricle, the left boundary by the right ventricle. In Ebstein's anomaly with signs of right-ventricular failure the heart is almost spherical in shape. The left ventricle does not change as a rule.

Ebstein's anomaly without cyanosis is often mistaken for *pericarditis with effusion* or for *congestive cardiomyopathy*. Pronounced cardiomegaly and weak pulsation of the heart are signs common to all three diseases. Ebstein's anomaly is distinguished from pericarditis by marked functional disorders of the right atrium. Electrocardiographic signs of right-atrial hypertrophy in combination with disturbed atrioventricular conduction are among the most characteristic signs of Ebstein's anomaly but are not encountered in pericarditis. No less important differential diagnostic significance should be attributed to the character of the heart sounds and murmurs. The diagnostic difficulties, nevertheless, are so great that they can only be overcome after angiocardiography and ventriculography.

It is far easier to distinguish Ebstein's anomaly from *valvular disease of rheumatic origin*, which is attended by tricuspid insufficiency, i.e. relative or organic insufficiency of the tricuspid valve. Right-ventricular failure takes a more benign course in rheumatic valvular diseases and in cardiomyopathies than in Ebstein's anomaly. The characteristic disturbances in water-electrolyte metabolism are often reversible. In many cases they disappear without a trace under the effect of long-term and consistent therapy. Patients suffering from Ebstein's anomaly usually die before ascites and hydrothorax develop. Death is sudden in this disease and is usually associated with attacks of terminal disorders of the heart rhythm.

Tricuspid stenosis occurs in conjunction with diseases of other valves in most cases. Developing in attendance to other heart diseases it leads to additional haemodynamic disorders. The liver is

the first to experience the telling effect of these new conditions of circulation. Its enlargement is the first clinical sign of oncoming heart failure.

Diastolic blood pressure is 5 to 7 mm higher, on the average, in the right atrium, than in the ventricle. This results in dilatation of the right atrium. On an anteroposterior radiograph the arch of the right atrium in a healthy human is no more than 2 cm beyond the right margin of the spine. The higher the pressure in the right atrium, the more its arch protrudes into the right pulmonary field and the sharper is the angle between the right atrium and the diaphragm.

The described shape of the heart with sharp distension of its shadow due to the right parts is called tricuspid. It is rather rare because tricuspid heart disease always develops in attendance to mitral stenosis or aortomitral valvular disease in which either the right ventricle or the right and left parts of the heart are enlarged. Simultaneous enlargement of both atria and ventricles leads to cardiomegaly. The shape of the heart in this case is spherical in the anteroposterior projection.

Considerable protrusion of the heart into the right pulmonary field is a constant X-ray sign of tricuspid heart disease but is also encountered in other heart diseases. According to some authors, the lower arch of the right contour of the heart may protrude into the right pulmonary field by 5 to 7 cm not only in tricuspid heart disease, but also in isolated mitral stenosis. Consequently, distension of the heart shadow to the right is merely a suggestion of a lesion of the tricuspid valve.

Enlargement of the right atrium (just as of the right ventricle) may best be appraised on radiographs taken in the second oblique position. In this position the enlarged right atrium narrows the retrosternal space, particularly in the upper part. Radiokymograms demonstrate signs of right atrial enlargement which are even more convincing.

The right lower contour of a healthy heart is formed by atrial waves, while the ventricular-type waves are only determined above the diaphragm for a distance of one or two bands. The zone of double-peaked waves of the right atrium is widened to six to eight bands in tricuspid stenosis. Complication of tricuspid stenosis by cardiac fibrillation leads to 'ventriculization' of the atrial waves on the radiokymograms. In such cases tricuspid stenosis is indistinguishable from tricuspid insufficiency.

Intravenous angiocardiography shows characteristic signs of tricuspid stenosis, namely, the formation of a dividing line between the cavities of the right atrium and the right ventricle. In severe tricuspid stenosis the contrast medium is retained in the right atrium for 20 to 26 seconds. Its retention for a shorter period of time

is also encountered in marked tricuspid insufficiency. The period of time that the right atrium is contrasted is also determined by the contractile function of the heart. The more severe the heart failure, the slower the blood flow, the longer the right atrium is contrasted.

The establishment of an exact diagnosis of tricuspid stenosis is of vital practical significance, especially for cardiosurgeons. This is why ventriculography is undertaken when the results of the diagnostic methods listed above are insufficiently convincing. In a healthy person the heart cavities are completely isolated during systole and because of this the contrast medium injected into the right-ventricular cavity cannot enter the right atrium. The flow of the contrast medium from the ventricle into the atrium is an authentic sign of tricuspid insufficiency.

Malignant and benign tumours lead to the development of chronic heart failure either by causing a direct unfavourable action on myocardial contractility or by creating conditions hindering normal heart activity as a pump. The basic mechanisms underlying heart failure are overloading of the heart by pressure or by the volume of the blood flow through it. These are often combined with disorders of the heart rhythm and short-term total cessation of the flow of blood through the heart. The clinical syndromes arising in this case may differ sharply from each other in their mechanisms and rate of development.

The achievements of modern medicine brought about a revision of the opinion that the prognosis of heart failure in tumours of the heart is unfavourable. Some of these diseases can be completely cured today and the correct and timely diagnosis is of importance that is not purely academic.

Chronic heart failure occurs both in primary and in metastatic tumours of the myocardium. In *primary myocardial tumour* heart failure is caused by the unfavourable effect of the new growth on heart contractility and rhythm. Sarcoma is the most common malignant tumour of the myocardium. Myxoma rhabdomyoma (Abrikosov's tumour) are the most frequently encountered benign tumours. Fibroma, lipoma and leiomyoma are much less frequent.

Malignant *tumours of other organs* may also lead to the development of heart failure. Extensive metastases of a malignant tumour to the lungs result in right-ventricular failure, which is a consequence of rapidly growing resistance to the flow of blood in pulmonary circulation. In the mechanism of its development this heart failure is similar to that in cor pulmonale. Overloading of the right ventricle is attended by hypertrophy which is mild, as a rule, because the disease takes a subacute course and the patient dies one or two months after signs of right-ventricular failure appear.

A subacute course of heart failure with the development of moderate right-ventricular hypertrophy is most common in carcinoma

of the stomach. Increased venous pressure, enlargement of the liver and the appearance of oedema of the lower limbs, and sometimes, ascites too in these patients are among the reliable signs of extensive metastatic carcinoma spread to the lungs. Muscat liver and mild right-ventricular hypertrophy are pathological confirmation of this diagnosis. Metastasis of a tumour to the peritoneum and the hepatic porta occurring simultaneously with metastasis to the lungs may cause the development of ascites. Hypoproteinaemic oedema is also observed in patients with carcinoma. The liver in such cases is of a hard consistency and is sometimes uneven. In heart failure the liver is uniformly enlarged, in metastatic tumours one of its lobes is enlarged. Atrophy and degeneration of the liver and myocardium are found on autopsy.

The development of heart failure in metastasis of a malignant tumour to the myocardium is attended by normal cardiac rhythm in some cases and by arrhythmias in others. Metastasis to the myocardium is particularly common in carcinoma of the lung and mammary gland. The clinical picture of heart failure in such cases, just as that of heart failure in primary sarcoma of the heart, is determined by the localization and the rate of growth of the tumour. The diagnosis of metastasis of a tumour in the myocardium may be suspected when signs of focal myocardial affection appear on the electrocardiogram and when the principal disease is complicated by a picture of subacute heart failure. It is very difficult to establish the diagnosis of primary sarcoma of the heart. The new growth is usually recognized only on autopsy.

Chronic heart failure is one of the late manifestations of *carcinoid tumour* (argentaffinoma). Depending on the localization of the primary tumour either the right or the left heart is affected.

Carcinoid tumour may grow in any part of the gastro-intestinal tract beginning with the stomach and ending with the rectum. The vermiform process is affected much more frequently than the other parts of the gastro-intestinal tract. The new growth develops somewhat less frequently in the ovary and hardly at all in the gall bladder and bronchi.

Carcinoid tumour secretes into the blood 5-hydroxytryptamine (serotonin) and most probably other humoral agents under the effect of which the picture of carcinoid affection of the heart develops. Pulmonary monoamineoxidase is capable of inactivating serotonin with the formation of 5-hydroxyindoleacetic acid. Humoral substances secreted by a tumour localized in the abdominal cavity first enter the right heart and cause its affection and only after this they are exposed to the action of pulmonary monoamineoxidase. The left heart is affected when the tumour arises from the bronchi and the substances secreted by it enter the left heart unaltered.

Diffuse fibrosis of the valvular structures develops under the effect of these substances. The free edges of the valves, the tendinous chordae and the apices of the papillary muscles are particularly sharply thickened. The subsequent shortening of the cusps, tendinous chordae and papillary muscles leads to in-

sufficiency of the valve, while adhesion along the lines of the commissures causes stenosis of the valvular orifices. Focal endocardial thickenings often form over metastatic tumours in the heart muscle.

Heart failure in carcinoid tumour always develops gradually and only in patients with a characteristic picture of the carcinoid syndrome. Signs of right-ventricular failure are the first to appear in most cases. The results of clinical examination show that it is usually caused by tricuspid insufficiency either alone or in combination with tricuspid stenosis. The findings of autopsy show that pulmonary stenosis is no less a common cause of heart failure in the carcinoid syndrome.

This discrepancy between the clinical and pathological findings is explained by the fact that it is easier for the pathologist to reveal the initial phenomena of pulmonary stenosis than those of tricuspid insufficiency when measuring the diameter of the orifices. Another important circumstance is that heart failure in pulmonary insufficiency is always right-ventricular.

Pulmonary stenosis leads first to hypertrophy and then to dilatation of the right ventricle. Distension of the valvular ring impairs the normal spatial relationship between the morphological structures of the valve. These disturbances result in relative tricuspid insufficiency the anatomical features of which are hard for the pathologist to determine, whereas its auscultative signs are easily heard and recorded on the phonocardiogram by the clinician.

While it is known that heart failure is a late complication of carcinoid tumour, the time when the valvular lesions develop remains enigmatic. More or less pronounced signs of tricuspid insufficiency are sometimes detected during the first examination of a patient in whom signs of carcinoid syndrome had recently appeared. In such cases it is unknown how long the tumour had existed.

Removal of the tumour before metastasis occurs results in the disappearance of the carcinoid syndrome, but signs of the valvular disease remain. Moreover, with time the signs of the heart disease become more pronounced because proliferation of fibrous tissue continues. Clinical, electrocardiographic and X-ray signs of right-ventricular hypertrophy appear gradually, venous pressure rises, the liver is enlarged and oedema and ascites develop. Medication with cardiac glucosides and diuretics causes brief improvement. Survival after the appearance of signs of heart failure is five years, on the average.

Heart failure in the carcinoid syndrome may be of a short duration. It may disappear after the tumour is removed. It has been suggested that right-ventricular failure develops in such cases under the effect of pulmonary hypertension which, in turn, is a consequence of the constrictive action of serotonin on the pulmonary arterio-

les. After removal of the tumour serotonin is no longer secreted in excessive amounts and pulmonary hypertension and with it the overload experienced by the right ventricle are relieved. As a consequence, right-ventricular failure disappears. The occurrence of paroxysmal dyspnoea in the carcinoid syndrome is likewise attributed to the effect of serotonin on pulmonary function.

Subendocardial growth of fibrous tissue causes various disorders of rhythm and conduction. Venous pulmonary hypertension, paroxysmal dyspnoea and temporary or permanent heart failure in such cases may be the consequence of cardiac fibrillation and have no cause-and-effect relation with serotonin. This mechanism may evidently be of independent significance only in patients who had undergone removal of a carcinoid tumour and in whom excretion of 5-hydroxyindole-acetic acid in the urine is normal.

Fibrous myocarditis developing under the effect of substances secreted by a carcinoid tumour may lead to affection of the heart valvular apparatus with the development of the syndrome of valve insufficiency or stenosis of the orifice and be the principal cause of the formation and advancement of heart failure. Patients with carcinoid tumour die either from the consequences of heart failure or from cachexia resulting from metastasis of the tumour to other organs. Apart from academic interest, the ability to identify the cause of the developing clinical manifestations of the disease may prolong the patient's life and relieve his suffering.

Disturbances of water-electrolyte metabolism in carcinoid tumour may be induced both by heart failure and by other causes. Metastasis of the tumour to the hepatic porta sometimes leads to the development of portal hypertension and its consequences, namely, ascites and oedema of the lower limbs.

Heart failure in carcinoid tumour is characterized by the development of isolated tricuspid insufficiency or tricuspid stenosis, whereas the most commonly encountered syndromes of tricuspid insufficiency and tricuspid stenosis of rheumatic origin are encountered in conjunction with mitral stenosis, as a rule.

Congenital isolated tricuspid and pulmonary diseases are distinguished from the corresponding valvular diseases in carcinoid tumour in the medical history and course. In patients with congenital valvular diseases the heart murmurs are heard from childhood whereas tricuspid disease and pulmonary stenosis appear in patients with carcinoid tumour no earlier than the other clinical signs of the syndrome.

Right-ventricular failure is sometimes induced by *myxoma of the right atrium*. During each systole the tumour moves into the right atrioventricular orifice. The haemodynamic consequences of this depend on the extent to which the tumour obstructs the flow of blood through the right atrioventricular orifice and the flow of

blood from the venae cavae into the right atrium rather than on the size of the tumour.

The clinical signs of right atrial myxoma resemble the signs of tricuspid stenosis in many respects. Systolic and diastolic murmurs are heard on auscultation, which differ from the corresponding murmurs of tricuspid stenosis in their variability. The variability in the duration and intensity of the diastolic murmur is particularly conspicuous. The right ventricle of the heart is sometimes enlarged. Moderate enlargement of the right atrium occurs in all cases of the disease.

Signs of right-ventricular failure in myxoma of the right atrium differ somewhat from the signs of such failure developing in decompensated tricuspid valvular disease.

A particularly characteristic feature is seen in the sharp increase of venous pressure detected at the very onset of the disease. In such cases the tumour is localized close to the orifice of vena cava superior and obstructs the flow of blood into the right atrium. As a result the picture of right-ventricular failure in myxoma of the right atrium may sometimes resemble the picture of constrictive pericarditis.

Embolism of the lungs by particles of the tumour or thrombi formed on its surface leads to recurrent haemoptysis and pulmonary infarction. These recurrent pulmonary thromboembolisms in conjunction with right-ventricular failure, subfebrile temperature or moderate fever and an increased content of globulins in the blood suggest rheumatic heart disease with a recurrence of rheumatic carditis.

In establishing the diagnosis one must bear in mind that rheumatic disease of the tricuspid valve occurs in conjunction with mitral stenosis, as a rule, whereas all cases of myxoma of the right atrium are never attended by pulmonary hypertension, enlargement of the left atrium or other signs of mitral stenosis. The characteristic signs of heart failure in myxoma of the right atrium are: syncope, palpitation, collapse, frequent complication by pulmonary infarction and an irrepressibly progressing course. Oedema of the subcutaneous tissue and ascites are usually mild. Heart failure in rheumatic heart disease usually follows an undulating course, and general weakness and oedema, but not syncope and collapse, gain prominence in the clinical picture.

The differential diagnostic signs mentioned above are not always sufficiently pronounced nor is it always expedient to await full clarification of the features of the clinical course taken by heart failure. The identification of an intracardiac tumour, as well as the exclusion of other causes of right-ventricular failure, may be achieved by means of special methods of examination (echocardiography, catheterization of the heart, and angiocardiography).

Chronic Cor Pulmonale

Hypertrophy of the right ventricle induced by pulmonary hypertension is called cor pulmonale, or pulmonary heart disease. Pulmonary hypertension arises under the effect of three factors: increased volumetric rate of pulmonary blood flow, obstruction of the flow of blood from the pulmonary veins, and diminished cross section of the pulmonary veins because of spasm or obliteration. The term 'chronic cor pulmonale' is applied only for designating those cases of right-ventricular hypertrophy the underlying feature of which is pulmonary hypertension induced by diseases listed in Supplement XIV-2. Failure of a pulmonary heart is diagnosed when the hypertrophied right ventricle is incapable of maintaining its debit on a level adequate to the volume of the venous blood flowing into it.

Pulmonary hypertension is manifested by dilatation of the pulmonary trunk and its pulsation in the second intercostal space, enlargement of the right atrium and hypertrophy of the right ventricle. The ECG signs of right-ventricular and right-atrial hypertrophy are typically high *P* waves in standard leads II and III. Hypertrophy of the right ventricle is detected by its pulsation in the fourth intercostal space at the left sternal edge and by a dull percussion sound over the lower third of the sternum. The second sound over the pulmonary artery is intensified and an ejection sound is sometimes heard here. Positive venous pulse and pulsation of the liver are evidence that tricuspid insufficiency has developed.

With advancement of pulmonary hypertension, the systolic murmur of tricuspid insufficiency is joined by the diastolic murmur of relative pulmonary insufficiency (Graham Steell murmur). A third sound of the right ventricle is sometimes heard. The sinus heart rhythm is preserved in the early stages of the syndrome, cardiac fibrillation is sometimes encountered in the late stages. Patients die from heart failure and its complications.

Recurrent thromboembolisms of the pulmonary artery are one of the common causes of cor pulmonale. The disease usually begins after childbirth or in pregnancy. Its origin is linked with thrombophlebitis of the lower limbs and the organs of the true pelvis or with prolonged use of oestrogenic contraceptives. Many Soviet authors allow that primary (essential) pulmonary hypertension similar to primary (essential) hypertension of the systemic circulation may exist. Its diagnosis is made by ruling out all diseases that are known to be capable of raising pressure in the pulmonary artery. Primary (just as thromboembolic) pulmonary hypertension is prevalent among females. Dyspnoea from physical exertion and syncope are the principal symptoms of the disease. Its objective signs are composed o

the pulmonary hypertension and tricuspid insufficiency syndromes.

In rare cases chronic cor pulmonale is induced by **amyloid deposits around the pulmonary vessels.** The diagnosis is established from the combination of the signs of right-ventricular failure with other manifestations of amyloidosis among which purpura, proteinuria, and impaired blood serum protein composition are most common. The disease occurs in elderly and old individuals, as a rule, and the purpura is discovered first in the intergluteal folds.

Some cases of **periarteritis nodosa** begin with affection of the pulmonary vessels. Cor pulmonale develops as a consequence and its failure usually sets in subacutely when there are other manifestations of periarteritis nodosa. Cor pulmonale failure also not infrequently takes a subacute course in **miliary metastasis of carcinoma** to the lungs ('carcinomatous lymphangitis') the diagnosis of which usually presents no difficulty. Other causes of cor pulmonale (parasitic diseases of the lungs, haemoglobinopathies) are extremely rare in the Soviet Union.

Insufficiency of the contractile function of chronic cor pulmonale is usually induced by diseases of the pulmonary parenchyma and air passages. **Chronic bronchitis and pulmonary emphysema** are easily distinguished by their morphological picture. The clinical difficulties of their differentiation coined the term 'obstructive pulmonary emphysema'. It is sometimes difficult to differentiate hypertrophy of the right ventricle from its failure and signs of pulmonary emphysema with frequently accompanying right-ventricular failure.

A barrel chest is accepted as a sign of pulmonary emphysema, but it is also encountered without emphysema. An emphysematous barrel chest differs from a barrel chest of a healthy person not in shape but in the fact that it does not move, or moves insufficiently during respiration. It is generally believed that disorders of cardiac rhythm are rare in pulmonary emphysema. There is nothing in our experience to confirm this. Pulmonary emphysema obscures the clinical signs of right ventricular hypertrophy. Disappearance of absolute cardiac dullness makes it difficult to palpate and see the pulsation of the right ventricle and the pulmonary artery. The heart sounds and murmurs are diminished in this case.

Oedema, distension of the subcutaneous veins on the neck, cough and haemoptysis are encountered in a patient with pulmonary emphysema irrespective of right-ventricular failure. In pulmonary emphysema the liver is often palpable because it is displaced downward. Its tenderness and oedema on the shins are always evidence of heart failure. Instead of skin 'warm cyanosis' common acrocyanosis is often found when pulmonary emphysema is combined with heart failure. Identical difficulties are encountered in making the diagnosis of right-ventricular failure in patients with **chronic in-**

terstitial pneumonias and **interstitial pulmonary sclerosis** combined with emphysema.

Right-ventricular failure in **tuberculosis of the lungs, pneumoconioses, sarcoidosis** and some other diseases listed in Supplement XIV-2 occurs only in the late stages of their development. Much less frequently it is the leading syndrome of these diseases. There is no difficulty in making the diagnosis of cor pulmonale in such cases.

Chronic cor pulmonale also develops in **kyphoscoliosis** and **marked adiposity.** In patients with kyphoscoliosis and heart failure, the lungs have a normal structure but they are small and the vascular bed is diminished, which proves to be particularly unfavourable during physical exercise. The small vertical dimension of the chest causes an irregular blood flow through the lungs. Reduced respiratory excursions of the lungs because of deficient mobility of the ribs are also significant.

Cor pulmonale and right-ventricular failure in adiposity are combined with alveolar hypoventilation. Obese patients with signs of heart failure are cyanotic and easily fall asleep even during conversation. Heart failure in these patients often occurs during acute respiratory diseases. The differential diagnosis of such heart failure usually presents no difficulty.

A clinical picture of secondary cor pulmonale with typical diffuse cyanosis develops in **severe mitral stenosis.** The need to differentiate cor pulmonale from mitral stenosis is explained by the considerable resemblance of their main clinical manifestations. Dyspnoea on movement is encountered in both diseases, whereas orthopnoea occurs only in patients suffering from heart disease. Both diseases are marked by enlargement of the right ventricle and systolic and diastolic heart murmurs may be heard in the precordial region in both. Electrocardiography records rotation of the electric heart axis to the right in both diseases, but *P* mitral waves (double-peaked in leads I and II, and biphasic in lead III) are found in mitral stenosis and *P* pulmonale waves (a tall *P* in leads II, III and aVF) in cor pulmonale. These differential diagnostic signs disappear in cardiac fibrillation which often complicates severe mitral stenosis. It is encountered in approximately 15 per cent of cases of cor pulmonale. A systolic murmur of relative tricuspid insufficiency may sometimes appear in cases of cor pulmonale with marked right-ventricular hypertrophy. This murmur may be erroneously interpreted as a mitral insufficiency murmur. A diastolic murmur of relative insufficiency of the pulmonary valve is sometimes heard in the left third-fourth intercostal space at the sternum in patients with cor pulmonale and severe pulmonary hypertension. Exactly the same murmur, i.e. Graham Steell murmur, is sometimes encountered in patients with mitral stenosis and high pressure values in the pulmonary artery.

The sound of mitral valve opening, or the opening snap, in mitral stenosis sometimes blends with the split second sound of cor pulmonale. On the phonocardiogram these sounds and murmurs are fairly easily distinguished, but they cannot always be distinguished by ausculation. To avoid a diagnostic error other methods of examination are resorted to.

The diseases that are compared differ in most cases in the medical history and in the extent of changes in the pulmonary tissue. The results of examining the shape of the heart are of particular value. The left atrium is enlarged in patients with mitral stenosis as a rule, but is normal in size in patients with cor pulmonale.

Abnormalities are sometimes also found in the lungs (emphysema, pulmonary fibrosis) of patients with mitral stenosis. Functional pulmonary tests also do not yield diagnostically reliable results in such cases. The final diagnosis is established only after complete study of haemodynamics. Blood pressure in the left atrium and pulmonary capillaries is elevated in mitral stenosis but normal in cor pulmonale.

Biventricular Heart Failure

Diseases of the Heart Muscle

Primary diseases of the heart muscle, which are generally divided into myocarditis and cardiomyopathy, are often the underlying factors of heart failure. Myocarditis is a term designating any inflammatory disease of the heart muscle. The term 'congestive cardiomyopathy' is used to name a primary lesion of the heart muscle of unrecognized aetiology (myocardosis) by some authors and to designate the late stages (outcomes) of chronic myocarditis by others.

Congestive cardiomyopathy is distinguished from myocarditis and myocarditic cardiosclerosis by the absence of its proven association with an inflammatory affection of the myocardium. Both in myocarditis and in congestive cardiomyopathy, marked dilatation of the heart is found by the time heart failure develops.

Concentric myocardial hypertrophy and hypertrophic subaortic stenosis are often encountered in one and the same family. Both diseases are characterized by progressive enlargement of the heart. It is possible that they are variants of the same disease. Heart failure is encountered in these diseases only in persons whose heart is drastically enlarged. Restrictive cardiomyopathy is a term generally accepted for a group of diseases in which the flow of blood to the heart is impaired. By the time heart failure develops in this disease, the heart is already either moderately or considerably enlarged.

Myocarditis

Since the turn of the century an acute inflammatory process in the myocardium of unknown aetiology has been called 'acute idiopathic myocarditis'. In the Soviet literature this form of myocarditis is linked with the names of Abramov and Fiedler. An acute onset and a rapid progressive course with a fatal outcome are the principal diagnostic criteria of interstitial myocarditis described by Fiedler in 1899. These criteria are evidently true only of cases of acute myocarditis.

The incidence of acute myocarditis with an unfavourable outcome has noticeably decreased in recent years, especially among the adult population. A sudden onset and irrepressibly progressive circulatory failure are now considered its main diagnostic criteria.

Inflammatory lesions of the heart muscle developing with no concomitant inflammation of other organs, and in which death is caused by the consequences of disturbed myocardial contractile function are generally included in the group of acute non-specific (idiopathic) forms of myocarditis.

In typical cases, myocarditis begins with fever which is at first usually mistaken for influenza or some acute respiratory infection. After two or three days of fever, a temperature becomes established at a subfebrile level and its duration may vary noticeably. In the period of subfebrile temperature, more or less marked unpleasant sensations or even pain are felt in the region of the heart and its functions are impaired. Enlargement of the heart, arrhythmias and phenomena of circulatory failure, at whatever stage of the disease they might appear, are always assessed as signs confirming the diagnosis of myocarditis.

Cardiomyopathies are commonly manifested by the syndrome of circulatory insufficiency, disorders of conduction, arrhythmias, recurrent thromboembolisms and chest pain of various localization which are also encountered in myocarditis. To avoid a diagnostic error it is probably necessary to differentiate cardiomyopathy from myocarditis and cardiosclerosis before all else.

The diagnosis of myocarditis is made with assurance if signs of concomitant pericarditis appear during the disease. This is most common in infection with Coxsackie viruses and echovirus and in affection with rheumatism and toxoplasmosis. The results of a series of tests for the titres of antistreptolysin and neutralizing antibodies against the most widely spread Coxsackie viruses, the Sabin and Feldmann test, complement fixation reaction or the identification of fluorescent antibodies in suspected toxoplasmosis may be of essential aid in making the diagnosis.

High eosinophilia is characteristic of Loeffler's endocarditis, while a combination of eosinophilia with periorbital oedema is typical of myocarditis developing in trichiniasis. Biopsy of the muscles may greatly help in the diagnosis of such cases.

Disorders of excitation and conduction developing during an infectious disease are always evidence of concomitant myocarditis. Particular diagnostic significance is attached to disorders of atrioventricular and intraventricular conduction. In some cases extrasystoles, particularly polytopic ventricular, indicate that myocarditis has developed.

The results of a series of electrocardiographic studies may greatly assist in detecting myocarditis. Despite the absence of arrhythmias, flattening or inversion of *T* wave and depression or noticeable elevation of *S-T* segment are sometimes detected on a series of ECG. Stable persistence of the abnormalities that had developed or their progression, particularly after the febrile period of the disease has come to an end, is generally accepted as a sign of myocarditis.

The high importance of these ECG abnormalities (which are, in essence, insignificant and non-specific) in establishing the diagnosis of myocarditis has recently been confirmed in observations over patients with a long survival period after heart transplantation. It was found that ECG changes are the earliest signs of the non-taking reaction. These changes are at first negligible, but sharper ECG abnormalities develop later and enlargement of the heart is noted.

The ECG abnormalities mentioned here are also encountered constantly in cardiomyopathies. They differ from the abnormalities in myocarditis in that they are more stable. The duration of *P-Q* segment, displacement of *S-T* segment and the depth and shape of wave *T* change quite rapidly in myocarditis, but remain completely or almost unchanged in cardiomyopathies.

Abatement of the inflammatory process in the myocardium is attended by changes in the character and force of the heart sounds and murmurs. In active myocarditis, the first sound is noticeably or sharply weakened, sometimes it acquires a specific velvety tone. The third heart sound appears before heart failure develops, but may disappear with the gradual abatement of the inflammatory process. The systolic murmur usually changes in duration and frequency composition with the development of the inflammation. In cardiomyopathies the heart sounds and murmurs maintain approximately the same force and frequency composition for very lengthy periods of time. With the development of heart failure, the third sound may sometimes be obscured by a mesodiastolic murmur, but the loudness of the first and second sounds does not change essentially in such instances.

Myocarditis is also distinguished from cardiomyopathy in its clinical course. In cardiomyopathies heart failure progresses and responds poorly to treatment. It grows more and more severe with every year. Death occurs from heart failure or from its complications. The prognosis of heart failure in myocarditis is often unfavourable but the disease may nevertheless terminate in the patient's recovery.

Acute and subacute myocarditis must sometimes be differentiated from *pericarditis with effusions.* The picture of marked blood stasis in the systemic circulation is equally characteristic of severe pericarditis and of severe myocarditis. These two diseases differ in the sequence of the appearance of some of the signs. Acute myocarditis leads to enlargement of the left ventricle and to the appearance of signs of left-ventricular failure at the onset as a rule. The clinical signs of right-ventricular failure usually appear simultaneously, or only when left-ventricular failure has already developed (dyspnoea, cough, congestive lungs). In pericarditis, the elevated pressure in the cavity of the pericardium first of all impairs the flow of blood from the veins of systemic circulation. The drainage of the vessels of pulmonary circulation is not disturbed in pericarditis, as a rule.

Enlargement of the liver and oedema of the lower limbs usually appear in myocarditis in patients who have dyspnoea and signs of pulmonary congestion. In pericarditis, hepatomegaly and oedema of the shins and feet appear earlier than dyspnoea and earlier than the signs of pulmonary congestion. High venous pressure and distension of the subcutaneous veins on the neck are always encountered in myocarditis only in patients who are gravely ill and are suffering from dyspnoea. In patients with pericarditis these signs may occur when there is no dyspnoea.

The differential diagnosis is made easier in some instances by the results of electrocardiography. A concordant elevation of *S-T* segment is often found in the initial period of acute pericarditis. A negative *T* wave appears in the later stages and the ECG of a patient with acute pericarditis becomes indistinguishable from the ECG of a patient with acute myocarditis in the shape of the *R-ST* complex. Disorders of conduction are hardly ever encountered in acute pericarditis, but are very typical of acute myocarditis. Elongation of *P-Q* segment, right or left bundle branch block, and frequent polytopic extrasystoles should always be accepted as evidence in favour of myocarditis. Cardiac fibrillation occurs in both diseases with about the same frequency.

The symptom of migrating oedema occurs only in pericarditis. Enlargement of the liver and pitting of the shins are found in the patient towards the end of the day. In the morning after a night's sleep pitting of the shins and feet disappears and the liver dimin-

ishes in size but puffiness of the face, neck and sometimes the whole upper half of the body develops.

The migration of oedema is explained by the fact that during the day, when the patient is in a vertical position, the effusion in the pericardial cavity compresses the vena cava inferior for the most part. At night, when the patient is lying in bed, the vena cava superior is compressed. Impaired flow of blood from vena cava superior leads to puffiness of the upper part of the body, whereas impaired flow of blood from vena cava inferior is conducive to the formation of oedema on the feet and shins. Oedema of this localization may also occur in myocarditis, but migration of oedema is never encountered.

The results of repeated X-ray examination help in many cases. The shape and dimensions of the heart change rapidly in acute pericarditis, but such rapid changes are not common in myocarditis. Sharp enlargement of the heart shadow is encountered both in pericarditis and in myocarditis.

In such doubtful cases the findings of radiokymography, angiocardiography and isotope scanning with radioactive human serum albumin (for determining the volume of the heart cavity) and radioactive colloidal gold (for determining the boundaries of the liver) sometimes help in establishing the diagnosis.

Echocardiography has been recently used for differentiating a drastically distended heart from pericarditis with effusion. The accumulation of fluid in the pericardial cavity is demonstrated by the appearance of a homogeneous space, which does not reflect waves, between the anterior chest wall and the anterior wall of the right ventricle or between the epicardium of the posterior wall of the left ventricle and the adjoining pericardium. The second sign indicating the presence of an effusion is diminished mobility of the posterior myocardial wall on the echocardiogram.

Congestive Cardiomyopathy

Congestive cardiomyopathy is manifested by heart failure. The early stages of this syndrome have not been fully studied. When the patient ultimately applies for medical aid his heart is already moderately or considerably enlarged and conduction is impaired which is often attended by disorders of heart excitation. Approximately one fourth of the patients have severe pain in the region of the heart which is erroneously interpreted as that of coronary origin.

Heart failure in cardiomyopathy takes an irrepressive progressive course and about two thirds of the patients die in about two years after its appearance. The survival period of the remaining patients

is more than five to six years. In this period they are treated for heart failure and its complications among which thromboembolisms are most hazardous.

From the findings of auscultation congestive cardiomyopathy is most frequently mistaken for *congestive mitral disease*. To avoid making such an error it must be borne in mind that although these two diseases have practically identical signs, the signs differ in the degree of their severity and in the character of their changes under the effect of therapy. Congestive cardiomyopathy, just as mitral disease, is marked by dilatation of both ventricles, electrocardiographic and X-ray signs of enlarged atria, and systolic and diastolic murmurs. The triple heart rhythm in cardiomyopathy may be mistaken for the triple rhythm of mitral disease.

In cardiomyopathies the systolic murmur arises as a consequence of distension of the valvular ring, i.e. it is related to murmurs of relative insufficiency of the mitral and tricuspid valves. It may occupy part of systole, but may also be pansystolic. On auscultation, it usually cannot be distinguished from the systolic murmur of organic insufficiency of these valves. A mid-diastolic murmur is heard in rare cases of cardiomyopathy. It may even be of a higher frequency than the diastolic murmur of mitral stenosis. In timbre and its position in diastole, this murmur may be confidently distinguished from the diastolic murmur of mitral stenosis without resorting to phonocardiography.

The third heart sound is sharply intensified practically in all cases of congestive cardiomyopathy. The fourth heart sound is encountered much less frequently. With the development of tachycardia, these sounds are approximated, creating the impression of a diastolic murmur. The principal purpose of auscultation consists in distinguishing the third heart sound from the opening snap of the mitral valve. At the normal rate of cardiac contractions, the third sound is easily identified by its pitch and its distance from the second heart sound. In cases of tachycardia its distance from the second sound may only be determined on the phonocardiogram. The opening snap is at a distance of 0.04-0.12 s and the third sound at a distance of 0.14-0.16 s from the aortic component of the second sound.

The differential diagnosis between congestive cardiomyopathy and mitral stenosis is a difficult problem, and it is not always possible to resolve it from the results of clinical examination. Besides the medical history, the following criteria often help to solve this task.

Successful treatment of heart failure by means of a salt-restricted diet, cardiac glycosides and diuretics leads to the disappearance of the gallop rhythm and the mesodiastolic murmur in a patient with cardiomyopathy. The opening snap and the diastolic murmur of

mitral stenosis remain after circulatory failure is corrected. Quite often they even become louder.

The diagnosis of mitral heart disease cannot be questioned if signs of mitral valve calcification are found on X-ray. X-ray examination is also invaluble from another standpoint. It allows a more or less regular enlargement of all parts of the heart (as it is observed in cardiomyopathy) to be distinguished from prevalent enlargement of the left atrium typical of mitral heart disease. Signs of pulmonary hypertension are usually clearly demonstrated in mitral diseases, but are either absent or moderate in cardiomyopathies.

Electrocardiography sometimes also aids in making the diagnosis. Signs typical of mitral stenosis (displacement of the electric axis to the right, overexertion of the right ventricle and its marked hypertrophy) are very rare in cardiomyopathy. The ECG changes typical of cardiomyopathies (intraventricular block, signs of focal myocardial changes, reduced voltage) are rarely encountered in mitral heart disease.

These two diseases are easily distinguished from each other by the results of echocardiography. The characteristic changes in the mobility of the anterior cusp of the mitral valve are described in the section 'Mitral Stenosis'. Congestive cardiomyopathy is characterized by total hypokinesia of the septum and the posterior wall of the left ventricle; this hypokinesia may be detected long before the signs of heart failure appear and it persists after congestion is corrected.

Heart failure in congestive cardiomyopathy is at times erroneously interpreted as *heart failure in atherosclerotic cardiosclerosis*. Heart failure in these two diseases often develops simultaneously with exacerbation of pain in the region of the heart.

Approximately one fourth of the patients with cardiomyopathy experience pain in the region of the heart. In all our cases these pains were dull, of long duration, and did not occur in attacks so typical of angina pectoris. According to the experience of other authors, the pain syndrome in cardiomyopathy is sometimes indistinguishable from that in angina pectoris of atherosclerotic origin. It is necessary to differentiate congestive cardiomyopathy from atherosclerotic cardiosclerosis with a history of *myocardial infarction* or even with a fresh infarct, when signs of heart failure develop and the ECG records focal myocardial changes in an elderly person experiencing such pain often with signs of moderate arterial hypertension.

Problems of this kind are often met with in emergency departments of large city hospitals. The physicians of these departments often lack both time and possibility to take a detailed medical history or re-examine the patient because of his grave condition and rapid development of collapse or pulmonary oedema. In such cases

the diagnosis has to be made on the basis of extremely brief information on the history and only one ECG taken on admission. Moreover, this ECG is drastically changed in cardiomyopathy, as a rule.

The abnormalities recorded on the ECG in congestive cardiomyopathy have no independent diagnostic significance, but a knowledge of them nevertheless helps in distinguishing this condition from myocardial infarction. The ECG voltage in standard leads is low, as a rule. The *Q* wave reflecting the beginning of septal excitation is not clearly traced, possibly because of diffuse septal fibrosis. The *R* wave is not demonstrated in leads V_1-V_3 and is often low in lead V_4. Left bundle branch block is often detected. Right bundle branch block is far less frequent. Delayed atrioventricular conduction is encountered very often; it is possibly caused by the effect of cardiac glycosides which are usually used in such cases. In approximately two thirds of the patients with congestive cardiomyopathy, *P* waves are high, broad and biphasic with a negative second phase. The *T* wave may be negative and/or biphasic.

Deformity of the *QRS* complex characteristic of cardiomyopathy rates special attention. It suggests that an anteroseptal myocardial infarction had been suffered in the past. In leads V_1-V_3 the ventricular complex has a *QS* shape while the height of *R* wave in lead V_4 is no more than 2 or 3 mm in some cases.

It is our opinion that the time of the appearance of chest pain is of no essential significance in the differential diagnosis between ischaemic heart disease and cardiomyopathies because in both diseases the pain syndrome occurs long before heart failure develops. It is important to determine the heart dimensions by the time the heart failure appears. In cardiomyopathy myocardial affection is always diffuse. As a consequence, heart failure in this disease is biventricular from the onset. The left and the right ventricles are simultaneously enlarged; enlargement of the liver and pitting of the shins are revealed together with paroxysmal dyspnoea. No signs of pulmonary congestion are usually found in this case.

In ischaemic heart disease, paroxysmal dyspnoea appears while the heart is still normal in size. Right-ventricular failure develops only after a more or less lengthy period of left-ventricular failure with recurrent attacks of cardiac asthma characteristic of it. Marked blood stasis in the lungs is encountered throughout this entire period. The formation of an aneurysm or extensive scarring of the left ventricle after infarction is a condition for the development of right-ventricular failure in ischaemic heart disease.

Information on a history of myocardial infarction in ischaemic heart disease is usually confirmed by the results of electrocardiography. Characteristic deformity of the ventricular complex with deep and broad *Q* waves is recorded on the ECG. The typical deformity of the ventricular complex in chest leads is recorded in cardio-

myopathy without the characteristic changes in *Q* wave in the standard and chest leads.

Echocardiography discloses the abovedescribed generalized hypokinesia in congestive cardiomyopathy. Atherosclerotic cardiosclerosis is always attended by segmental disorders of mobility of the left ventricular walls. Hypokinesia and akinesia in the scarred areas of the myocardium (e.g. in the posterolateral wall of the left ventricle) are encountered simultaneously with compensatory hyperkinesia of at least one remaining unaltered myocardial area (e.g. intraventricular septum of the heart). A consistent study of the mobility of the separate myocardial segments discloses this characteristic sign of ischaemic heart disease complicated by atherosclerotic cardiosclerosis.

Rare Diseases

Rapidly advancing heart failure predominates in the clinical picture of some metabolic diseases and diseases of unrecognized aetiology which are marked by simultaneous involvement of the endocardium and myocardium: endocardial fibrosis (Davis' disease), South African endomyocardiopathy (Bekker's disease) and fibroplastic parietal endocarditis (endocardial fibroelastosis). Heart failure is not only the principal syndrome of these diseases but the most common cause of their unfavourable outcome. Death is usually caused by pneumonia or pulmonary infarction developing in conjunction with heart failure. Disorders of conduction and heart rhythm are the second constant sign of these diseases and causes of frequently occurring sudden death.

Fibroplastic parietal endocarditis, endocardial fibroelastosis and, judging from reports, Davis' and Bekker's diseases are very often complicated by the formation of parietal thrombi in the heart cavities. Recurrent thromboembolism into the organs of pulmonary and systemic circulation is just as characteristic of heart failure in these diseases as disorders of rhythm and conduction.

Fibroplastic parietal endocarditis. Progressive heart failure refractory to all modern methods of treatment and combined with eosinophilia was described for the first time by Loeffler who called it 'fibroplastic parietal endocarditis with eosinophilia'. Later it turned out that apart from the endocardium this disease always affects the myocardium and the arteries of many internal organs.

Cicatrization of connective tissue in the foci of inflammation leads to deformity of the papillary muscles and the tendinous chordae of the mitral and tricuspid valves and to the formation of mitral and tricuspid insufficiency. The left ventricle is involved more than the right, as a rule.

The disease prevails among males from 30 to 50 years of age. It follows a subacute or chronic course. With the appearance of heart failure, the survival period usually does not exceed one year. The disease is often ushered in by eosinophilia to which signs of heart affection develop in attendance later. The blood eosinophil content may reach 30-70 per cent. Eosinophilic arteritides are found not only in the heart but in other organs too. Multiple vasculitides may noticeably change the clinical manifestations of the disease, making the diagnosis difficult.

Despite the pronounced phenomena of heart failure the heart in fibroplastic parietal endocarditis remains small, as a rule. Pulmonary congestion and pulmonary hypertension do not develop evidently because the myocardium of both ventricles is involved simultaneously. Hepatomegaly in these patients is easily explained by heart failure, but splenomegaly is usually induced by recurrent thromboembolism the source of which is in the heart cavities. The same cause underlies recurrent pneumonia and pulmonary infarction which are often complicated by pleurisy with effusion.

Disorders of atrioventricular or intraventricular conduction are recorded on the ECG at the beginning of the disease. Disorders of cardiac rhythm develop in attendance to them in the later stages. Ventricular extrasystoles and attacks of supraventricular tachycardia appear first. Cardiac fibrillation develops in graver cases.

Heart failure occurring in a patient with a small heart and with no signs of pulmonary congestion indicates the possibility of constrictive pericarditis. Marked leucocytosis with eosinophilia and fever are evidence against this diagnosis. Heart murmurs are only encountered in annular pericarditis with calcification, the signs of which are usually detected on the radiographs.

Endocardial fibroelastosis. Two forms of endocardial fibroelastosis are distinguished: the primary form in which thickening of the endocardium is the only abnormality in the heart and the secondary form in which thickening of the endocardium occurs simultaneously with other heart diseases, for instance, aortic stenosis, ventricular septal defect, coarctation of the aorta, and stenosis of the pulmonary artery.

Primary fibroelastosis is one of the causes of heart failure in infants. Sometimes the disease is encountered among adults. It is manifested clinically by heart failure, arrhythmias and embolisms.

Cardiomegaly is noted in all cases of endocardial fibroelastosis following a chronic course. The heart sounds are usually diminished in this type of the disease. A murmur appears when the cicatricial tissue impairs the function of the papillary muscles. It is usually weak in intensity and occupies only part of the systole. Pain in the region of the heart and shortness of breath are the first symptoms which make the patient apply for medical assistance.

In about six or twelve months all kinds of heart rhythm, disorders and signs of severe right-ventricular failure (hepatomegaly, oedema of the lower limbs, ascites) develop in attendance to the phenomena of left-ventricular failure. Parietal thrombi form in the cavity of the left ventricle and become the sources of embolisms to the arteries of the systemic circulation. Heart failure sometimes responds to treatment, but the improvement is short-lived. The patient died from heart failure which is often complicated by pneumonia, terminal arrhythmia or recurrent thromboembolisms.

Endocardial fibroelastosis of the chronic type has to be differentiated from myocarditis, aortic stenosis, mitral insufficiency, congestive cardiomyopathy, pericarditis with effusion, and amyloidosis of the heart. By the time that right-ventricular failure develops in these diseases the heart is already enlarged while its pulsation is noticeably or sharply diminished. Endocardial fibroelastosis may set in abruptly and take the course of an acute disease resembling Abramov-Fiedler's myocarditis.

The ECG in endocardial fibroelastosis records signs of left-ventricular hypertrophy with characteristic changes of *T* wave in the chest leads. The *P* waves may be high, broad and spiked. In this the ECG in endocardial fibroelastosis differs from the ECG in aortic stenosis. In distinction from pericarditis with effusion, the voltage of the ECG waves in endocardial fibroelastosis stays high. In distinction from myocarditis, disorders of conduction are very rare in endocardial fibroelastosis. In myocarditis the shape of the tracings on the electrocardiogram changes rapidly. The size, direction and shape of *T* wave alter particularly frequently. Despite the arrhythmia, the shape of the separate ECG complexes in endocardial fibroelastosis is stable.

Signs of inflammation typical of myocarditis are absent in endocardial fibroelastosis. Body temperature is normal and neither leucocytosis nor increased ESR nor changes in the composition of the globulin fractions in blood serum are found. The results of endocardial biopsy of the myocardium may greatly help in the differential diagnosis of these diseases. In recent years this method of diagnosis is winning ever more popularity.

The diagnosis of myocarditis by identifying autoantibodies (antibodies reacting with myocardial organ-specific antigens) in circulation by immunofluorescence deserves special attention. Unfortunately this method has not won full acknowledgement in the clinics as yet. We could not find reports on the results of this method in the diagnosis of endocardial fibroelastosis in the literature available.

Cardiomegaly with right-ventricular failure and various arrhythmias are often encountered in isolated mitral insufficiency or in

mitral disease with prevalence of insufficiency. It is relatively easy to make the differential diagnosis between mitral insufficiency and endocardial fibroelastosis. The first heart sound is of normal intensity in endocardial fibroelastosis but may be diminished in mitral insufficiency. The systolic murmur occupies only part of the systole in endocardial fibroelastosis and the entire systole in mitral insufficiency. The left atrium is not enlarged in endocardial fibroelastosis with a preserved rhythm but is often enormous and never of normal size in mitral insufficiency. A properly taken medical history may prove to be of essential assistance in the differential diagnosis of these two diseases.

Knowledge of the medical history makes the differential diagnosis between aortic stenosis and endocardial fibroelastosis much easier. Cardiomegaly is found, as a rule, by the time that right-ventricular failure develops in a patient with aortic stenosis. The characteristic systolic murmur may not be heard because of the small blood flow through the valves. The auscultative picture in such cases of aortic stenosis is hard to distinguish from that of endocardial fibroelastosis. The retention of the sinus rhythm and the absence of thromboembolisms distinguish heart failure in aortic stenosis from heart failure in endocardial fibroelastosis.

Pericarditis with effusion is usually ushered in by fever. Signs of toxicosis and heart tamponade predominate in the clinical picture of the disease by the time that abundant effusion forms in the pericardium. Disorders of water-salt metabolism are mild in this period of the disease. Neither disturbances of heart rhythm nor thromboembolisms typical of endocardial fibroelastosis are found in this period of pericarditis with effusion. Echocardiography, X-ray with heart scanning, and exploratory puncture of the pericardium may be conducted in doubtful cases for detecting fluid in the pericardial cavity.

It is most difficult to differentiate endocardial fibroelastosis from congestive cardiomyopathy. Cardiomegaly, disorders of heart rhythm, the occurrence of sudden death, and heart failure are typical of both diseases. Endocardial fibroelastosis is distinguished from congestive cardiomyopathy by a more unfavourable course of heart failure and lower incidence of intraventricular conduction disorders. Heart failure in endocardial fibroelastosis is irreversible from the very onset. Even after quite a long period of intensive treatment, the disorders of water-salt metabolism can be corrected, but the patient's working capacity is not restored. The attained improvement is short-lived, as a rule. Most patients die 12 months after right-ventricular failure appears. In cardiomyopathy heart failure takes a more favourable course.

Amyloidosis of the Heart

Two mechanisms of right-ventricular failure in amyloidosis can be distinguished. The deposit of amyloid around the pulmonary vessels leads to the development of cor pulmonale whose deficient contractile function may be the cause of right-ventricular failure with increased venous pressure in systemic circulation, hepatomegaly, oedema and ascites. Amyloid deposits in the heart itself are manifested by the picture of left-ventricular failure which is soon joined by right-ventricular failure.

Cough, paroxysmal dyspnoea and often orthopnoea develop in the period of left-ventricular failure. Pain in the region of the heart is often noted, which, together with changes in the ECG ventricular complex, frequently are the cause of an erroneous diagnosis of anteroseptal myocardial infarction. Cardiomegaly, a systolic murmur, and gallop rhythm are found in the patient by the time right-ventricular failure develops.

Amyloidosis of the heart is one of the manifestations of generalized amyloidosis with a characteristic high albuminuria, malabsorption syndrome, increased content of globulins and especially their macrodispersed fractions in blood, macroglossia, and the nephrotic syndrome. Enlargement of the heart in combination with low ECG voltage and disorders in myocardial conduction and excitation are evidence of involvement of the heart in amyloidosis.

Heart failure in persons over 70 years of age is usually a consequence of atherosclerotic cardiosclerosis, calcinosis of the aortic or mitral valves and diseases of the lungs. Other causes of heart failure at old age (amyloidosis, endocarditis lenta, tumour of the heart) are much less frequent. If heart failure develops for the first time at old age and its cause is not clear, aortic stenosis and painless myocardial infarction must be ruled out before all else.

The first occurrence of *ischaemic heart disease with myocardial infarction* of an extent inducing right-ventricular failure is hardly possible after the age of 70. The clinical picture of such vast infarct in the myocardium sharply differs from the picture of amyloidosis of the heart. Heart failure develops gradually and insidiously in amyloidosis of the heart but sharply within a few days or weeks after the onset of the disease in myocardial infarction. A patient with extensive myocardial infarction (heart failure develops only after extensive infarction) can specify the date when he fell ill. It remains uncertain as to when amyloidosis began. Hepatomegaly and oedema appear first and only after that the physician begins to seek their cause.

Angina pectoris often precedes myocardial infarction. The dimensions of the heart are usually normal when the infarct occurs

and heart failure develops for the first time in atherosclerosis of the coronary arteries, whereas in amyloidosis the heart is always enlarged.

In most cases of amyloidosis the ECG records displacement of the electric axis to the left, low voltage of *QRS* complexes and *T* waves in the standard and chest leads, and delayed atrioventricular conduction. The *R* waves in the right chest lead usually have a small amplitude and the whole ventricular complex often takes a *QS* shape. In combination with negative *T* wave these abnormalities often prove to be the cause of hyperdiagnosis of myocardial infarction.

This error may be avoided if it is borne in mind that ECG abnormalities appear long before heart failure in amyloidosis of the heart, whereas in myocardial infarction and in atherosclerotic cardiosclerosis the characteristic ECG changes develop simultaneously with the clinical manifestations of the disease. Moreover, in myocardial infarction the ECG undergoes characteristic changes with time, whereas in amyloidosis it remains stable. The results of other methods for identifying myocardial infarction and amyloidosis may help considerably in solving this diagnostic problem. Particular significance should be attached to changes in the activity of the cardiac isoenzymes, creatine phosphokinase and lactate dehydrogenase, and the characteristic changes in the blood serum protein composition.

Heart failure in amyloidosis follows an irreversible progressive course. Therapeutic measures produce only short-term improvement. Heart failure in atherosclerotic cardiosclerosis may disappear completely if treated intensively. We discussed the differential diagnosis between ischaemic heart disease and amyloidosis in greater detail only because our own experience shows that this is a difficult problem.

Right-ventricular failure in *aortic stenosis* is always of a secondary character. It develops after a more or less lengthy period of left-ventricular failure, i.e. always in marked pulmonary congestion. Heart failure in amyloidosis, just as in other cardiomyopathies, is in most cases biventricular from its very onset. In amyloidosis hepatomegaly and oedema of the subcutaneous tissue may appear with no signs of congestion in the lungs.

The characteristic systolic murmur of aortic stenosis is heard long before heart failure develops.

The systolic murmur in amyloidosis is usually auscultated only over the heart apex, it is never diamond-shaped or pansystolic and is not attended by a thrill. It is not referred to the neck vessels. Amyloidosis and aortic stenosis differ noticeably from each other in the characteristic ECG changes and in the blood serum protein composition. Cardiac fibrillation is practically never encountered

in aortic stenosis but is a frequent complication of amyloidosis.

Endocardial fibroelastosis is distinguished from amyloidosis mainly by the patient's age. Amyloidosis is a disease of old age whereas endocardial fibroelastosis usually afflicts the young and middle-aged. Diverse disorders of cardiac rhythm and tendency to thromboembolisms are components of the principal diagnostic triad of endocardial fibroelastosis. Thromboembolic complications are not among characteristic features of amyloidosis. Biopsy of the gum or mucous membrane of the large intestine proves very helpful at times in establishing the diagnosis of amyloidosis. Purpura often occurs in amyloidosis but is encountered neither in atherosclerotic cardiosclerosis nor in endocardial fibroelastosis.

Left-ventricular Failure

Mitral Stenosis

The incidence of mitral stenosis among females is about double that among males. There is no difficulty in making the diagnosis in most cases. It can often be established when the patient is examined for the first time. It is far more difficult to determine the severity of the stenosis and decide whether there are concomitant diseases of other heart valves. Obstruction to the flow of blood from the left atrium is the initial and main link in the circulatory disorders in mitral stenosis. In marked mitral stenosis the left atrium is always dilated and the blood pressure in it is elevated. When the blood pressure in it rises to the level of 20-25 mm Hg, the function of the sphincters in the orifices of the pulmonary veins is impaired. The blood pressure in the pulmonary veins and capillaries becomes the same as in the left atrium. Conditions thus exist for the seeping of fluid from the capillaries into the interstitial tissue of the lungs.

Blood pressure is always higher in the lower lobes of the lung than in the upper lobes and Kerley's lines (signs of oedema of the connective tissue stretching between the pulmonary lobules) are therefore demonstrated earliest in the lower lobes. The more pronounced the oedema of the interstitial tissue, the more rigid is the lung and the more difficult becomes oxygen transport from the alveoli to the pulmonary capillaries. In mitral stenosis the endobronchial veins function as collaterals through which blood flows from pulmonary into systemic circulation. Ruptures of varicose endobronchial veins lead to haemoptysis and the formation of infarcts in the lung.

Cardiac fibrillation is a late complication of mitral stenosis. It occurs at first in short paroxysms, but becomes continuous later. Prolonged existence of increased blood pressure in the left atrium

and pulmonary veins leads to the development of pulmonary hypertension which most authors consider to be the consequence of active spasm of the pulmonary arterioles. Resistance in pulmonary circulation increases drastically, creating 'a second barrier' to the flow of blood, this time from the right ventricle into the left atrium. Pulmonary hypertension is of a functional character initially. Reorganization of the vascular system of pulmonary circulation begins later and arteriovenous anastomoses and end arteries develop.

High pressure in the pulmonary artery causes overloading of the right ventricle, which is the main cause of its failure. Affection of the tricuspid valve, cardiac fibrillation and exacerbation of an inflammatory process in the myocardium are other causes of right-ventricular failure.

In approximately 58 per cent of cases mitral stenosis develops after an attack of rheumatic fever. The characteristic deformity of the valve and the clinical picture of the disease develop not immediately after the attack, but 3 to 25 years later. The difference in the duration of the latent period is explained by the fact that in some cases mitral stenosis is consequent upon recurrent valvulitis, while in others, as is believed by many authors, it develops under the effect of haemodynamic factors. In most cases the symptomatic period of the disease begins with dyspnoea which is at first experienced only during physical exercise. A sudden deterioration in the patient's condition occurs less frequently and its common underlying factors are acute respiratory infection, embolism and the onset of cardiac fibrillation.

Paroxysmal dyspnoea, sometimes developing into oedema of the lung, occurs for the first time in a patient with mitral stenosis usually under the effect of an increased load on the heart, for instance, in pregnancy and physical exertion. Acute respiratory failure often developing in influenza and other acute respiratory diseases is particularly hazardous. Haemoptysis is sometimes the first complication which makes the patient with mitral stenosis call on a doctor. This complication, which alarms the patient, tends to recur although in most cases there is no immediate danger to life. The older the patient, the larger the left atrium, the longer the duration of mitral stenosis, the more frequent is cardiac fibrillation. Some patients can put their finger on the date cardiac fibrillation began from the characteristic sensation of palpitation, whereas in others this complication begins and develops without producing any symptoms. Cardiac fibrillation is among the frequent causes of heart failure in mitral stenosis.

Embolism of the vessels of pulmonary and systemic circulation sometimes occurs before noticeable dyspnoea appears. With the development of cardiac fibrillation, the frequency of thromboembolisms increases considerably. The hazard of embolisms is particu-

larly great in the first days and weeks following the onset of cardiac fibrillation. Thrombosis of the left atrium is most common, though it is not the only cause of embolisms to the vessels of the systemic circulation. Thrombotic deposits on the valves may be the source of embolisms. The clinical picture of embolisms is determined by the size and localization of the emboli. Embolism of the cerebral and lower limb vessels is encountered most commonly. Embolism of the mesenteric, renal, splenic and coronary arteries of the heart is a much less frequent occurrence. It is often difficult to establish its diagnosis, because of the acute clinical picture of the developing functional disorders of the involved organ.

Thrombi in the cavities of the right heart and veins of the lower limbs and pelvic organs are the sources of embolism of vessels of the pulmonary circulation. A parietal thrombus in the pulmonary artery is a rare source. Most pulmonary thromboembolisms are multiple. Recurrent thromboembolisms may lead to heart failure or be the cause of its irresponsiveness to the therapeutic measures applied.

Cardialgia is observed in many cases of marked mitral stenosis; the pains are sometimes of a pleural or pericardial character. It is at times extremely difficult to distinguish them from angina pectoris. The pains disappear after successful mitral commissurotomy. Many clinicians investigated the mechanisms of these pains. In summarizing the results of their studies, it may be stated that the angina pectoris syndrome in marked mitral stenosis is caused by coronarosclerosis or by concomitant aortic stenosis.

The diagnosis of mitral stenosis is established on the basis of a constellation of signs the main of which are the auscultative triad, a change in the shape of the heart, and pulmonary hypertension.

The triad of auscultative signs of mitral stenosis is composed of a loud first sound, a diastolic murmur and the opening snap. Unfortunately, cases of mitral stenosis are encountered in which any one of the listed components of the triad, or all three, may be absent. Most frequently the diastolic murmur and the opening snap cannot be detected.

The loud first sound is often the first sign suggesting the possibility of mitral stenosis. The presumption is all the more convincing if other causes of intensification of the first heart sound are ruled out. Among these causes are thyrotoxicosis, tachycardia, arterial hypertension, and accelerated atrioventricular conduction, for instance in the Wolff-Parkinson-White syndrome. An intensified first sound together with delayed atrioventricular conduction is a characteristic sign of mitral stenosis. The first heart sound is normally loud or even diminished in cases of mitral valve calcification, high pulmonary hypertension and left atrial thrombosis.

The mitral valve opening snap sometimes cannot be heard because

of a loud diastolic murmur following it; sometimes it is difficult to distinguish the opening snap from a split second sound. The diastolic murmur of mitral stenosis is usually not transmitted to the base of the heart or to the sternum. The opening snap unassociated with the murmur can often be auscultated at the sternal base. Splitting of the second sound is best heard over the base of the heart in the second or third intercostal space at the left sternal edge. The opening snap is equally clearly audible over the base and over the apex of the heart. It is heard most clearly halfway between the heart apex and the sternal edge.

Depending on the rate of cardiac contractions, the opening snap is recorded on the phonocardiogram 0.04-0.12 second after the beginning of the second heart sound. When the heart rate varies between 70 and 90 per minute, the opening snap is usually recorded 0.07-0.08 second after the second sound.

The interval between the components of the split second sound increases during inspiration and decreases during expiration, thus reflecting the fluctuations in the blood filling of the right ventricle. The duration of the interval between the beginning of the second heart sound and the opening snap remains the same during inspiration and expiration. It decreases noticeably only in association with fluctuations in the rate of cardiac contractions. The rate of contractions is sharply reduced after phenylephrine hydrochloride or other vasopressor agents are prescribed. This results in an increase in the interval between the second heart sound and the opening snap, but has no effect on the size of the interval between the components of the split second sound. Changes in reverse occur after tachycardia which is induced by physical exercise, but this test is less reliable insofar as differential diagnosis is concerned.

The fixed wide splitting (which does not change with the respiratory phases) of the second heart sound is not encountered in pure mitral stenosis. It is typical of atrial septal defect, right bundle branch block, stenosis of the pulmonary artery, severe mitral insufficiency, and sharply pronounced primary or secondary pulmonary hypertension. The detection of wide splitting of the second sound in a patient with undoubted mitral stenosis should be accepted as an argument, and very reliable at that, indicating the combination of mitral stenosis with one of the diseases listed above.

The opening snap is always evidence of a block to the flow of blood from the left atrium into the left ventricle. The third heart sound reflects the unhindered and rapid filling of the left ventricle at the beginning of diastole. Both additional sounds originate at the beginning of diastole. An audible third sound completely rules out the diagnosis of mitral stenosis. This is precisely why it is necessary to distinguish these sounds from one another.

In a patient lying on his left side the third sound is best heard over the region of the apex beat, while the opening snap is most clearly heard about halfway between the apex beat and the left sternal edge. The third sound is always of low frequency and, in most cases, not loud. The opening snap always contains a high-frequency component. It is louder and shorter (more abrupt) than the third sound.

Sometimes the third sound in mitral insufficiency is as loud as the opening snap, but in such cases they are usually distinguished easily from each other on the phonocardiogram according to the moment they appear in the cardiac cycle and according to their relation to the apex beat.

Simultaneous palpation and auscultation disclose that the third heart sound arises at the same time as the apex beat, whereas the opening snap precedes the apex beat. The third sound originates 0.14-0.16 second after the second heart sound. The size of the interval between these two sounds does not depend on the rate of cardiac contractions. The opening snap occurs 0.04-0.12 second after the second sound; the length of this interval is not constant and varies noticeably depending on the changes in the rate of cardiac contractions.

The opening snap is caused by sudden cessation of blood flow behind the tensed cusps of the mitral valve and by the fluctuations of the cusps themselves. It is heard only if the cusps are mobile. The opening snap is encountered not only in mitral stenosis, but also in some other diseases. Its occurrence in mitral stenosis is linked with the rigidity of the anterior cusps of the mitral valve. It is possible that in myxoma the opening snap arises as a consequence of the direct impact of the tumour against the valve cusps.

Attempts have been made to determine mitral valve mobility by cineangiocardiography. Unfortunately, it turned out that after the contrast medium had been injected into the pulmonary artery, its concentration in the left heart cavities was not sufficient enough for the cusps to be outlined. Ventriculography often demonstrates the mobility of the mitral valve, but this method today has been replaced in many cases by echocardiography. The anterior cusp of the mitral valve is much larger than the posterior cusp. Because of its large surface it reflects the ultrasonic waves well and thus makes it possible to watch its movements easily. The rate of mitral cusp movement in mitral stenosis is always slowed down.

The anterior cusp of the mitral valve in a healthy heart moves forward and backward for the most part. During diastole it makes three movements, two of which (at the beginning and end of the diastole) are in a forward direction, and the third (in the middle of diastole) is directed backward. Blood pressure in the left atrium is increased during entire diastole and the anterior cusp is therefore con-

stantly tensed and displaced forward, while its second (forward directed) movement is always less marked than in a healthy person.

Unfortunately, this disturbance in the mobility of the anterior cusp is of no diagnostic significance in itself because it is encountered not only in mitral stenosis, but also in other diseases. It is recorded with particular constancy in aortic valvular diseases which are often attendant to mitral stenosis, in hypertrophic subaortic stenosis, and in cases of marked pulmonary hypertension. This difficulty can be overcome by recording the movements of the posterior cusp which in mitral stenosis moves just like the anterior cusp. In aortic valvular diseases, hypertrophic subaortic stenosis, and pulmonary hypertension, the movement of the posterior cusp of the mitral valve does not change.

The altered shape of the heart characteristic of mitral stenosis is explained by enlargement of the left atrium and hypertrophy of the right ventricle. The size of the left atrium is demonstrated best by X-ray. In the frontal plane, the enlarged left atrium is seen as a bulging of the third arch on the left heart border.

The left atrium is mainly enlarged to the back and to the right. Its posterior right wall is adjoined by the middle segment of the oesophagus. The enlarged atrium displaces the oesophagus to the back and to the right. The radius of the oesophageal displacement arch is a good reflection of the size and shape of the left atrium. Oesophageal displacement along the arch of a small or medium-size radius is typical of mitral stenosis. Displacement of a contrasted oesophagus is best demonstrated in the first oblique position. Small enlargement of the left atrium cannot be demonstrated by X-ray. In appraising the results of the examination it should be borne in mind that the degree of the oesophageal curvature depends on the depth of inspiration at the moment when the X-ray is taken.

The transverse dimension of the heart is normal even in severe mitral stenosis. The right ventricle is enlarged only in pulmonary hypertension. This enlargement is diagnosed most reliably by palpation, percussion, and electrocardiography. Considerable right-ventricular enlargement may also be detected by X-ray.

Distension of veins in the upper lobes and constriction of veins in the lower lobes are found in the period of venous hypertension of the lung. The findings of isotope scanning indicate that blood shunting into the upper pulmonary lobes underlies this sign. This sign is encountered only in mild mitral stenosis with left atrial blood pressure ranging from 15 to 20 mm Hg. When the diameter of the right descending branch exceeds 16-17 mm the condition is called dilatation of the pulmonary arteries. The combination of dilatation of the central arteries with sharply constricted peripheral arteries is typical of severe pulmonary hypertension. Venous engorgement of long-standing sometimes leads to the development

of pulmonary haemosiderosis. Small foci of ossification appear in the lung in very rare cases.

The left atrium is enlarged to the back and to the left in mitral stenosis. As the result of the deviation of its axis to the back the atrial wave in the standard leads is broad and often double-spiked. In leads V_1 and V_2 it is either negative or biphasic with a negative second phase. In displacement of the left atrial axis to the left or upward the atrial wave in leads V_5 and V_6 is defined more clearly than under normal conditions; in the first standard lead it is higher and broader than in the third lead.

In appraising these changes in *P* wave it should be taken into account that they are not seen in every case of mitral stenosis and may be encountered in some diseases marked by affection of the left ventricle. Quite broad and notched atrial waves are also sometimes encountered in individuals with no signs of a heart disease.

Hypertrophy of the right ventricle develops when mitral stenosis is complicated by pulmonary hypertension. Deviation of its electric axis to the right is its most sensitive index. In normal duration of the ventricular complex, deviation of the electric axis by more than 100 degrees and the ratio of the *R* and *S* waves values in the first chest lead of more than unity are encountered only in marked hypertrophy of the right ventricle. Blood pressure in the pulmonary artery in such cases usually fluctuates between 35 and 80 mm Hg. It should be remembered, however, that the ECG may be absolutely normal even in marked mitral stenosis.

Many methods for determining the severity of mitral stenosis have been suggested, but none (even catheterization of the heart cavities) can be regarded as faultless. Determination of mitral stenosis severity according to the duration of the *Q*—first sound or second sound—opening snap interval was very popular in its time. With the accumulation of material it was established that these intervals were determined by the rate of cardiac contractions, fluctuations of the atrioventricular gradient, the rate of pressure elevation in the left ventricle, the rate of left-ventricular relaxation, and many other clinically immeasurable factors, rather than by the severity of the stenosis. This method yields quite satisfactory results in repeated examination of the patient and may be recommended for a follow-up of the evolution of mitral stenosis.

X-ray signs of venous hypertension in pulmonary circulation are only encountered in moderate mitral stenosis with the area of the orifice exceeding 1.5 cm^2. Signs of interstitial pulmonary oedema are usually found in patients suffering from dyspnoea at rest and are evidence of marked stenosis. A conclusion to the contrary would not be rightful, for the absence of interstitial oedema does not rule out severe mitral stenosis.

Mitral valve mobility is preserved in mild mitral stenosis, where-

as in severe mitral stenosis the valve is rigid. Palpatory and electrocardiographic signs of right-ventricular hypertrophy always testify to the severity of mitral stenosis. Echocardiography appraising the mobility of the mitral valve cusps provides indirect information on the severity of mitral stenosis.

The mildest cases of mitral stenosis follow an asymptomatic course. Their diagnosis is usually based on the results of auscultation. Electrocardiography and X-ray examination disclose no changes in the heart. The opening snap is often absent or is only auscultated when the patient lies down, whereas in a vertical position it disappears and only the loud character of the first sound draws attention on auscultation. The short presystolic murmur is either not auscultated or mistaken for splitting of the first sound. After physical exercise, however, the presystolic murmur grows louder. A soft pansystolic murmur of mitral insufficiency is heard in most cases of this 'auscultative mitral stenosis'.

A pansystolic murmur over the heart apex may be the only murmur auscultated in pronounced mitral stenosis, particularly in one marked by a picture of severe and protracted heart failure. This phenomenon is explained by considerable right-ventricular hypertrophy. The left heart border in such instances is formed by the right ventricle and the heart apex is rounded and displaced to the left costal margin. The frontal radiograph gives the impression of left-ventricular hypertrophy, whereas actually the left ventricle is ousted to the back and loses contact with the chest wall. As a result, the diastolic murmur of mitral stenosis is inaudible.

In distinction from the systolic murmur of mitral insufficiency the systolic murmur in tricuspid insufficiency is intensified during inspiration and diminished during expiration. It is not transmitted to the left axilla though it may be heard well over the heart apex. It usually intensifies noticeably after the patient inhales amyl nitrite. A diagnostic error is often corrected by studying the ECG on which signs of isolated right-ventricular hypertrophy are found. In a few cases of mitral stenosis deep S waves are recorded in leads V_2 and V_3 which are sometimes erroneously interpreted as evidence of left-ventricular hypertrophy. In severe isolated mitral stenosis with sharp deviation of the electrical axis to the right, deep S waves are recorded not only in leads V_2 and V_3 but are registered up to lead V_6 where the R/S ratio reaches 1.5.

In some cases of mitral stenosis pressure in the pulmonary artery equals the pressure in the aorta. The radiographs of such patients demonstrate sharp dilatation of the central pulmonary arteries and amputation of their peripheral branches with the formation of a characteristic picture of a 'charred tree'. The findings of percussion, palpation, and electrocardiography are indicative of marked right-ventricular hypertrophy. The diagnosis of primary pulmonary

hypertension, pulmonary fibrosis, or Eisenmenger's syndrome is sometimes made during the first examination of these patients.

All our patients suffering from mitral stenosis with severe pulmonary hypertension were admitted to the clinic with severe heart failure. An attempt to sit up in bed caused dizziness and marked dyspnoea. Not only the mucous membranes, but the skin were cyanotic and the limbs were cold. The cardiac rhythm was normal in two patients. Neither the loud first sound not the opening snap was auscultated in them. The diastolic murmur was also absent. A recently developed heart failure was resistant to therapy. It was only the medical history that pointed with no room for doubt to the fact that we were dealing with cases of mitral stenosis which was actually 'aphonic'. Autopsy revealed mitral stenosis with calcification of the valve and drastically increased thickness of the right ventricle.

The clinical picture of mitral stenosis is quite typical and the correct diagnosis can usually be made at the patient's bedside. Diastolic and systolic heart murmurs are simultaneously auscultated in most cases of mitral stenosis. In such instances it is essential to identify the origin of the systolic murmur. A differential diagnosis usually has to be made between mitral stenosis and mitral insufficiency.

Insufficiency of the mitral valve attendant to the stenosis is mostly manifested by a systolic murmur and changes in the character of the first heart sound and the size and shape of the heart. The apex beat in cases of pure mitral stenosis may be displaced to the left, in prevalence of mitral insufficiency it is displaced to the left and downward. This is explained by left-ventricular hypertrophy which is clearly detected in prevalence of mitral insufficiency.

X-ray in mitral insufficiency demonstrates enlargement of the left atrium and left ventricle. In pure mitral stenosis it shows enlargement of only the left atrium. The predominance of mitral insufficiency is displayed on the ECG by signs of left-ventricular hypertrophy, whereas predominance of mitral stenosis by signs of right-ventricular hypertrophy.

In pure mitral stenosis the systolic murmur is also not heard at all. A systolic murmur attendant to mitral insufficiency may be auscultated during entire systole, i.e. it may continue without interruption from the first sound to the beginning of the second sound. Sometimes it occupies only the initial part of systole. This murmur is usually of a diminishing character. It is loud at the beginning of systole, diminishes by its end and is not heard before the beginning of the second sound. A late systolic murmur is commonly of an intensifying character. It begins a short time after the first sound and continues to the second sound. The systolic murmur of mitral insufficiency is clearly transmitted to the left axilla and intensifies

after medication with phenylephrine hydrochloride or some other vasopressor agent. The experience of surgeons shows that the more intensive the systolic murmur, the sharper is mitral insufficiency attendant to the stenosis.

In predominance of mitral insufficiency the first heart sound is usually somewhat diminished. The opening snap is auscultated in some cases of pure mitral insufficiency. The exact character of the lesion in such cases may be revealed by catheterization of the heart, selective angiocardiography, intracardiac phonocardiography, and echocardiography.

In rare cases mitral stenosis has to be differentiated from *aortic insufficiency*. Aortic valvular diseases are obscured by signs of mitral stenosis existing in the same patient. In other cases they themselves lead to the development of functional mitral stenosis.

A diminishing diastolic murmur with maximum audibility in the third and fourth intercostal spaces at the left sternal edge often proves to be either a murmur of aortic insufficiency or a murmur of relative insufficiency of the pulmonary valve. If this murmur is auscultated in a patient with enlargement of the left ventricle and electrocardiographic signs of its hypertrophy this murmur is attributed to aortic insufficiency. If a patient has signs of severe pulmonary hypertension, intensified parasternal pulsation of the right ventricle, and electrocardiographic evidence of right-ventricular hypertrophy, then the diminishing diastolic murmur of this localization is linked with insufficiency of the semilunar valves of the pulmonary artery. In relative insufficiency of the pulmonary valve, diastolic pressure in arteries of systemic circulation is always normal, whereas in aortic insufficiency it may be either normal or low.

Flint's presystolic murmur and a ventricular gallop rhythm are auscultated in some cases of aortic insufficiency. In other words, signs of relative mitral stenosis appear in the patient. The peripheral signs of aortic insufficiency are usually very clearly defined in such cases as a result of which the diagnosis is made much easier.

The classical picture of angina pectoris, just as fainting fits during physical exercise, are rather common in the *aortic-mitral heart disease*. They are absolutely untypical of pure mitral stenosis.

In isolated mitral stenosis the heart is not enlarged. In combined aorto-mitral heart disease the left ventricle is enlarged and its apex is rounded and often displaced to the sixth intercostal space. In distinction from pure mitral stenosis the waist of the heart in aorto-mitral disease is preserved and sometimes even emphasized. Intensified pulsation of the commonly mildly distended ascending aorta is another characteristic feature.

In severe heart failure the left ventricle may be enlarged because of its myogenic dilatation, while the pulsation of the ascending

aorta may be weakened because of reduced systolic output. The typical picture of mitral-aortic heart disease develops only after the signs of heart failure abate somewhat.

In some cases electrocardiography helps very much in differentiating pure mitral stenosis from mitral stenosis combined with aortic insufficiency. Deviation of the electrical heart axis to the left in what to all appearances is undoubted mitral stenosis, just as a dextrogram revealed in a picture of aortic heart disease, is often the point of departure from which the entire diagnosis is reviewed and reappraised.

The prognosis concerning the rehabilitation of a patient under the effect of non-operative therapy in pure mitral stenosis sharply differs from a similar prognosis in mitral stenosis combined with organic lesions of the tricuspid valve. The abovestated explains the importance of the earliest possible differentiation of these diseases. The differential diagnosis between mitral stenosis and *tricuspid stenosis* in practice actually always comes down to a differential diagnosis between isolated mitral stenosis and mitral stenosis existing in conjunction with pure or predominant tricuspid stenosis.

The clinical picture of mild tricuspid stenosis is obscured for a long time by the symptoms and signs of simultaneously existing mitral disease. In these patients tricuspid stenosis is recognized by a sensation of discomfort in the right hypochondrium after a meal, rapid satiation, eructation, and heaviness in the right hypochondrium or epigastrium after a meal. These symptoms appear before hepatomegaly is discovered. Unfortunately, they provide the grounds only for suspecting tricuspid stenosis.

The objective signs of severe tricuspid stenosis, namely, distension of the neck veins, a positive venous pulse, enlargement and systolic pulsation of the liver, cyanosis, subicteric skin, and other findings of physical examination are indistinguishable from the signs of the commonly concomitant tricuspid insufficiency. The findings of electrocardiography are also insufficient for distinguishing tricuspid stenosis from organic or relative tricuspid insufficiency developing simultaneously with it.

As a result of prolonged treatment for heart failure in mitral stenosis, oedema and ascites disappear and the liver grows smaller. The venous pressure decreases as a rule, and often becomes normal. If mitral stenosis is combined with tricuspid stenosis the venous pressure remains elevated even after the signs of heart failure disappear. The high differential diagnostic significance of the results of angiocardiography proceeds from the fact that long-term contrasting of the right atrium with the formation of a clear demarcation line between the cavities of the right heart is a characteristic sign of tricuspid stenosis which is easily detected in a patient after the

disappearance of heart failure. In a patient with isolated mitral stenosis, the signs of tricuspid insufficiency disappear simultaneously with heart failure.

Isolated *tricuspid insufficiency* is an exceptionally rare occurrence, and in the practice it is not tricuspid insufficiency that must be differentiated from mitral insufficiency, but mitral stenosis with tricuspid insufficiency from mitral stenosis with mitral insufficiency. The results of examination of the patient help in making the differential diagnosis between these combinations of heart diseases before all else. Dyspnoea on physical exertion and, sometimes, orthopnoea are typical signs of mitral insufficiency, but are not characteristic of tricuspid insufficiency. A patient with tricuspid insufficiency can lie low in bed. He usually complains not of shortness of breath from physical exertion, but of weakness which prevents him from doing some physical work. The subcutaneous veins on the neck are tense in patients with tricuspid unsufficiency and a positive venous pulse is easily found on their inspection. The liver is enlarged, sometimes considerably. Its palpation may reveal expansive systolic pulsation. Sharp enlargement of the liver without oedema of the subcutaneous tissue is only encountered in tricuspid insufficiency. In mitral insufficiency these signs are not found.

The systolic murmur in the diseases compared may be heard well at the attachment of the fifth rib to the sternum but the murmur of mitral insufficiency is transmitted clearly to the left axilla whereas the murmur of tricuspid insufficiency is not transmitted to the left of the heart apex. In patients with a maintained sinus rhythm and with no signs of severe heart failure, the systolic murmur of tricuspid insufficiency is noticeably intensified on inspiration. This sign is not found in patients suffering from cardiac fibrillation and severe heart failure. The systolic murmur of mitral insufficiency diminishes on inspiration and intensifies after expiration. In mitral insufficiency the heart is usually enlarged in length, whereas in tricuspid insufficiency the transverse dimension of the heart is predominantly enlarged. The results of atrial electrokymography are even more important. Mitral insufficiency is characterized by expansive pulsation of the left atrium, and tricuspid insufficiency by marked pulsation of the right atrium.

The results of electrocardiography are of considerable aid in some cases. Sharply pronounced signs of right-ventricular hypertrophy are always found in mitral stenosis with organic or relative tricuspid insufficiency. Right atrial enlargement is manifested by high *P* waves in leads II, III and aVF and biphasic *P* wave (from the first positive phase) in lead V_1. Signs of left-ventricular hypertrophy appear on the ECG in more or less severe mitral insufficiency. In doubtful cases the final diagnosis is established from the findings of heart catheterization.

In practice, organic tricuspid insufficiency most commonly has to be differentiated from relative tricuspid insufficiency, and mitral stenosis with mitral insufficiency from mitral stenosis with tricuspid insufficiency. Relative tricuspid insufficiency differs from organic in the degree of manifestation and reversibility of the signs and not in the presence or absence of this or that sign. Intensive therapy of heart failure with cardiac glycosides, diuretics and a salt-restricted diet is the best method for their differentiation. Under the effect of such treatment the signs of relative tricuspid insufficiency disappear, while the signs of organic insufficiency remain.

Atrial Septal Defect

Congenital heart diseases marked by the shunting of blood from systemic into pulmonary circulation may be asymptomatic for a lengthy period of time. This is particularly common in cases of atrial septal defect, ventricular septal defect, and persistent ductus arteriosus. In a progressive course, these diseases are complicated by pulmonary hypertension with the appearance of which overloading of the right ventricle by pressure occurs in addition to its overloading by the increased volume of blood. The size of this overloading is proportional to the volume of blood flowing through the shunt and the level of blood pressure in the pulmonary artery. Progressive overloading of the right ventricle leads to its failure.

The clinical picture of right-ventricular failure in congenital heart diseases closely resembles the picture of heart failure in mitral stenosis. Our experience obliges us to stress the particular difficulty of the differential diagnosis between heart failure in mitral stenosis and that in atrial septal defect.

With the development of heart failure the clinical picture of atrial septal defect alters noticeably. The clockwise rotation of the heart makes the systolic murmur audible not only in the second and third intercostal spaces, but also in the fourth interspace and even over the heart apex. The appearance of deep *Q* waves in standard leads II and III is also explained by this. Fixed and wide splitting of the second sound is maintained only for the time the shunt is functioning. With cessation of the flow of blood through the defect, the fixed splitting of the second sound is replaced by a sharply intensified second sound which is sometimes mistaken for an accentuated second sound over the pulmonary artery characteristic of mitral stenosis.

These two diseases are complicated as a rule by cardiac fibrillation and pulmonary hypertension. It is important to keep in mind that pulmonary hypertension is always more severe in atrial septal defect marked by signs of heart failure than in mitral stenosis. Considerable dilatation of the pulmonary trunk and right pulmonary

artery is especially typical of atrial septal defect. Evidence of sharp enlargement of the right atrium and right ventricle is always found on radiographs and on electrocardiograms. In atrial septal defect the size of the left atrium remains normal for a long time. It is slightly enlarged only with the development of cardiac fibrillation.

Cardiac fibrillation appears in a case of atrial septal defect when the patient is between the age of 30 and 40. Moderate enlargement of the left atrium develops in attendance to pulmonary hypertension. Physical exertion causes severe dyspnoea in these patients. In a balanced shunt, the mobility of the cardiac septum becomes normal and echocardiography cannot yield additional information on the cause of dyspnoea and cyanosis which appears from time to time.

In discussing the differential diagnosis between mitral stenosis and atrial septal defect it must be taken into account that enlargement of the left atrium is less and dilatation of the pulmonary artery is sharper in atrial septal defect than in mitral stenosis. These two diseases also differ in their course. Patients with mitral stenosis often have a history of recurrent congestive failure, which is never encountered in patients with atrial septal defect. Catheterization of the heart is resorted to for establishing the final diagnosis in difficult cases.

Myxoma of the Left Atrium

Myxoma is a benign tumour which, according to various authors, accounts for 35-50 per cent of all primary tumours of the heart. It occurs just as often among males as among females. In about 75 per cent of cases the tumour is found in the left and in about 25 per cent in the right atrium. The tumour usually has a pedicle attached to the atrial septum in the region of the oval fossa. It is hard or jelly-like in consistency, round or oval in shape, and its surface is even or covered with villi.

The clinical manifestations of myxomas are very diverse. They may be conditionally separated into signs reflecting the general body reaction to the tumour growth, signs caused by the unfavourable effect of the tumour on the heart, and signs consequent upon thromboembolic complications.

The initial clinical manifestations of atrial myxoma have not been sufficiently studied. The diagnosis is made or presumed when during each systole the tumour penetrates the atrioventricular orifice narrowing it and sometimes even obstructing it completely. When the tumour is in the left artium, haemodynamic disorders are of the type occurring in mitral stenosis, but if the tumour is in the right atrium, they are of the type of tricuspid stenosis.

Heart failure with elevated arterial pressure, hepatomegaly, and oedema of the lower limbs is the most common clinical syndrome of myxoma of the heart. It is encountered in 90 per cent of patients. Moderate pulmonary hypertension joins these signs when the tumour grows in the left atrium. All patients with myxoma of the heart suffer from dyspnoea, general weakness, and rapid fatiguability. In approximately a third of the patients these signs are combined with complaints of chest pain, palpitation experienced from time to time, and a tendency to faint, i.e. with complaints typical of decompensated heart diseases.

Myxoma of the heart and *rheumatic heart diseases* are similar not only in the subjective picture of the disease, but in the results of objective examination. Left atrial myxoma closely resembles mitral stenosis, whereas myxoma of the right atrium is more like tricuspid stenosis. Since rheumatic heart diseases are more common than heart myxoma, heart failure induced by the tumour is often mistaken for heart failure caused by rheumatic heart disease. Myxomas grow in the left atrium three times as often as in the right and a differential diagnosis must therefore be made between left atrial myxoma and mitral stenosis. In some cases, clinical methods suffice for reliable differentiation of these two diseases; in others they substantiate the need to resort to special methods.

In mitral stenosis heart failure occurs several years after the onset of the disease, as a rule. Most patients are well aware of their disease for a long time and often describe recurrences of rheumatic carditis suffered in the past, the appearance of heart failure and its duration and severity, their health in the periods of remission, and, sometimes, a past history of rheumatic polyarthritis.

Heart failure in myxoma of the heart has no such undulating course. Dyspnoea, hepatomegaly and oedema appear within the first year after the onset of the disease. They are usually, mild, but despite treatment never disappear completely. Heart failure in myxoma of the heart is characterized by a progressive and not a recurrent course. Patients have no history of rheumatic polyarthritis, and heart diseases had never been diagnosed in them.

These two diseases also differ in the patient's appearance. By the time that heart failure develops in mitral stenosis the patient has characteristically rosy cheeks. All our patients with myxoma of the heart had no such signs, although the signs of heart failure were clearly manifested in them.

The auscultative signs of mitral stenosis and myxoma of the left atrium are similar, but on repeated auscultation inconstancy of the diastolic murmur in myxoma of the left atrium may nonetheless be noted. Its intensity and duration change not only when the patient changes from a horizontal to a vertical position, not only when he changes his position in bed, but without any obvious

cause. The diastolic murmur may be absent in aphonic mitral stenosis, but when audible it is distinguished by its stable character.

The systolic murmur in left atrial myxoma is much louder than the diastolic murmur. Such a combination of murmurs in mitral stenosis is evidence of a simultaneous existence of mitral insufficiency with hypertrophy of both right and left ventricles characteristic of it. The natural enlargement of one or both ventricles in myxoma is not encountered. Myxoma may produce no electrocardiographic or X-ray signs of ventricular hypertrophy, which never happens in mitral disease.

By impairing the blood flow through the atrioventricular orifice myxoma may sometimes lead to its total or almost total arrest. As a result, depending on the extent of cerebral ischaemia, the patient experiences attacks of dimness, dizziness, and even syncope. These symptoms and signs are encountered in approximately one third of patients with myxoma of the heart. They occur when the patient changes position in bed, in changing from a horizontal to a vertical position, but may occur for no obvious reason. Postural syncopes are encountered in mitral stenosis only when attended by high pulmonary hypertension. In myxoma of the heart they may be observed when there are no clear signs of pulmonary hypertension and even when there are no signs of right-ventricular hypertrophy.

Pronounced right-ventricular hypertrophy and left atrial enlargement are characteristic signs of right-ventricular failure in mitral stenosis. When there are no signs of active rheumatic carditis, then right-ventricular failure in mitral stenosis is always encountered in association with manifest pulmonary hypertension. Myxoma of the left atrium is characterized by the incongruence of the severity of right-ventricular failure and manifest pulmonary hypertension.

Some complications developing in mitral stenosis also occur in myxoma of the left atrium, but with due consideration given to the details of their origin the proper approach to their diagnosis can, sometimes, be found. In mitral stenosis heart failure hardly ever occurs without cardiac fibrillation. Embolism of the arteries of the systemic circulation is only encountered in mitral stenosis complicated by cardiac fibrillation or rheumatic carditis. Heart failure in myxoma of the left atrium usually develops with a normal heart rhythm. Embolism of the vessels of the systemic circulation is found in approximately 40 per cent of cases of left atrial myxoma and may occur with a normal heart rhythm.

Growth of the tumour is sometimes attended by fever, changes in the blood serum protein composition, and the development of anaemia which is usually moderate. The extent of these signs reflecting the general body reaction differs from case to case. Body temperature may be subfebrile or persist at a level of 38-39°C. Depending

on the severity of anaemia, the manifest character of thromboembolism, and shifts in the protein globulin fractions in the blood serum a clinical picture develops resembling that of endocarditis lenta or mitral stenosis complicated by a recurrence of rheumatic carditis. The final diagnosis of myxoma of the left atrium may be established in such doubtful cases only by means of special methods of examination.

Angiocardiography with injection of a contrast medium into the right atrium, pulmonary artery or left atrium demonstrates a characteristic filling defect in the atrium. The combination of this sign with a typical clinical picture of the disease allows the true cause of heart failure to be identified with assurance and not only to save the patient from death, but to restore his working capacity.

Echocardiography has lately been used for establishing the diagnosis of myxoma of the heart. As reported by Feigenbaum (1973), this method provides for a reliable diagnosis of myxoma of the heart. Examination of the same patient by means of angiocardiography and at the same time by echocardiography produced results which coincided in all cases. An intracardiac tumour was found on operation in all of these patients. It was removed and morphological examination showed it to be a myxoma.

Summarizing the data listed, it may be stated that the diagnosis of mitral stenosis may be established reliably from the findings of physical methods of examination in most cases. Diagnostic errors are usually made because the diastolic murmur is absent, the patient is insufficiently examined or complications or diseases are present which obscure the signs of mitral stenosis.

It is difficult to diagnose mitral stenosis in patients with aortic valvular disease. The mesodiastolic murmur which is often heard in these diseases is frequently interpreted mistakenly as a sign of mitral stenosis. This typical error may be avoided if it is accepted as a rule to establish the diagnosis of mitral stenosis only when the patient has a mesodiastolic murmur with a preceding opening snap. Presystolic intensification of the diastolic murmur and a loud character of the first sound may be absent in the patient with congestive failure. If they do not appear after the congestion is corrected, echocardiography or catheterization of the heart with blood pressure measurement in the left atrium is advisable for making an exact diagnosis.

A diagnostic error is made because the results of X-ray examination have been interpreted incorrectly, when signs of relative mitral insufficiency are mistaken for signs of mitral stenosis. To avoid such an error it should not be forgotten that mitralization of the heart in aortic insufficiency, and particularly in congenital stenosis of the aortic orifice, occurs long before decompensation appears.

It is commonly known that the diagnosis of aphonic mitral steno-

ses, i.e. stenoses in which the diastolic murmur is not auscultated, is a difficult problem. This happened particularly often in severe heart failure and in sharply increased rate of cardiac contractions. It is advisable to postpone the final diagnostic conclusions until tachycardia and signs of heart failure disappear under the effect of treatment. If typical signs of mitral stenosis do not appear even after successful treatment, catheterization of the heart is indicated for making the exact diagnosis.

Mitral Insufficiency

Mitral insufficiency is one of the clinical syndromes with which a physician has to deal from the time he is a medical student until the end of his professional career. Modern methods of examination revealed the exclusive complexity of haemodynamic disorders in this syndrome, whereas clinical observations disclosed the extreme diversity of the symptoms and signs arising in such a case. In generalizing the new information on the clinical picture and pathological physiology of mitral valve it may be stated with no exaggeration that he who has a sound knowledge of mitral disease knows half the science of cardiology. In the present section we discuss only those facts accumulated to date which are directly related to the differential diagnosis of mitral insufficiency.

The mitral valve apparatus consists of four parts: the valvular ring, two cusps, the chordae tendineae, and papillary muscles. The valve functions normally only if the intact cusps have a normal width and mobility, if the mitral ring on contraction during a systole reduces the area of the left atrioventricular orifice approximately to two thirds of its size during a diastole, if the chordae tendineae are of normal length and their endings are evenly distributed along the edges and on the surface of the cusps, and if the papillary muscles contracting synchronously with the left ventricle are capable of holding the valve cusps in a state of approximately the same tension during entire systole. Disturbance in the function of any part of the valvular apparatus leads to mitral insufficiency.

Congenital and acquired mitral insufficiency are distinguished in clinical practice. The characteristic symptoms and signs of acquired mitral insufficiency occur acutely in some cases or develop gradually in others. Mitral insufficiency of rheumatic origin takes a chronic course as a rule. It begins with thickening and shortening of cusps and tendinous chordae. Lesions of other parts of the valvular apparatus are mostly encountered in ischaemic heart disease, cardiomyopathy, myocarditis, endocarditis and congenital developmental anomalies of the connective tissue. This type of mitral insufficiency occurs abruptly in most cases, though later it may follow a chronic course.

Pure or predominant mitral insufficiency is commonly encountered. Various cases of this disease differ sharply in the extent of haemodynamic disorders and in the clinical course. The congenital form of mitral insufficiency is very rare. Acquired mitral insufficiency is often a consequence of mitral commissurotomy in our time. Among other causes of mitral insufficiency we can name the following in the order of their diminishing incidence: rheumatic fever, bacterial endocarditis, lesion of the papillary muscles, hypertrophic cardiomyopathy, ventricular septal defect, Pierre Marie-Bekhterev's disease, systemic lupus erythematosus, and tumours of the atrium.

Correction of congestive failure in this valvular disease is achieved at the cost of hypertrophy of the left parts of the heart the extent of which is determined to a great measure by the volume of regurgitation.

Chronic mitral insufficiency. The clinical manifestations of mitral insufficiency are very diverse. A systolic murmur over the heart apex and slight left-ventricular hypertrophy may be the only signs of the disease. Enlargement of the left atrium and left ventricle is found in mild or moderate insufficiency. The hypertrophied left ventricle is capable of sustaining the minute volume at a normal level even when half of its systolic output enters the left atrium. The period of total compensation of the disease may be of considerable length.

The advancement of the disease leads to left-ventricular failure whose first symptoms are weakness and rapid fatiguability on exertion. Pulmonary hypertension is less sharp in mitral insufficiency than in mitral stenosis because the flow of blood into the left ventricle during diastole is not obstructed. Dyspnoea occurs only on exertion at first, but later it is experienced even at rest. In this period of the disease, physical exercise induces attacks of dry, agonizing cough. Attacks of paroxysmal dyspnoea sometimes occur.

Long stints of work while overcoming raised pressure in the pulmonary artery lead to hypertrophy of the right ventricle and ultimately to its failure. With the appearance of signs of right-ventricular failure the disease takes an unfavourable course. The more marked left atrial hypertrophy becomes, the more often is recurrent decompensation of this disease.

A systolic murmur is the principal diagnostic sign of mitral valve insufficiency of any origin. It occupies entire systole. It begins simultaneously with the first sound, obscures it, and ends after the second sound, which indicates that the regurgitation of blood is continued at the beginning of diastole. The diastolic murmur usually lasts no longer than 0.25 second.

In affection of both cusps of the valve, the systolic murmur is usually audible most clearly over the heart apex and is transmitted

to the left axilla. When only one of the cusps is involved the systolic murmur usually takes a diamond shape. In affection of the posterior cusp, it spreads mainly to the upper part of the chest, whereas in affection of the anterior cusp the murmur spreads to the back, to the interscapular space.

The following features of the systolic murmur must be taken into account in making the differential diagnosis. In severe mitral insufficiency of rheumatic origin, the systolic murmur always catches up with the second heart sound. Termination of the systolic murmur before the second sound occurs only in mild mitral insufficiency, usually of non-rheumatic origin. This is mostly a functional murmur or a murmur of aortic stenosis transmitted to the apex. The first heart sound in such instances is normal or even intensified.

Respiratory splitting of the second sound is maintained in mild mitral insufficiency; wide splitting of this sound is often recorded on the phonocardiogram in cases of severe mitral insufficiency. It results from shortening of systole of the left ventricle which discharges the blood contained in it simultaneously into the left atrium and the aorta. It is difficult to distinguish wide splitting of the second sound from the opening snap recorded approximately in 10 per cent of cases of severe mitral insufficiency, and from the third heart sound. These sound phenomena are sometimes identified only from the results of simultaneously recorded phonocardiogram, apex cardiogram and the contour of the pulse wave in the aorta or carotid artery.

The findings of electrocardiography in mitral insufficiency are usually of minor significance in the differential diagnosis. In many cases of this disease the degree of left-ventricular hypertrophy may be determined more precisely according to localization, extent and force of the apex beat. The findings of echocardiography provide evidence only of increased blood flow through the mitral valve. They are valuable in ruling out mitral stenosis and in detecting some cases of non-rheumatic mitral insufficiency. The results of X-ray examination are far more significant; in severe mitral insufficiency it may demonstrate an enlarged left atrium, bulging of the third arc along the left contour of the heart shadow, and abnormally large angle formed by the tracheal bifurcation. In acute mitral insufficiency, these signs may be absent.

In a small volume of regurgitation, chronic mitral insufficiency is attended neither by marked hypertrophy of the left ventricle, nor by considerable enlargement of the left atrium. Such cases of mitral insufficiency often have to be distinguished from mitral stenosis. The difficulty in the differential diagnosis between these diseases may be overcome in most cases before special examinations are undertaken. The extraordinary practical importance of this

problem, as we see it, justifies the information presented below on the main difficulties encountered in the differentiation of these two diseases at the patient's bedside.

Before all else, it is most expedient to draw attention again and again to the circumstance that a systolic murmur in the precordial region does not rule out the diagnosis of pure mitral stenosis. The systolic murmur may be induced in mitral stenosis by relative tricuspid insufficiency and concomitant aortic stenosis and mitral insufficiency. In some cases of mitral stenosis, the systolic murmur arises in the pulmonary artery and is of pure functional origin.

Thus, although the systolic murmur is the principal sign of mitral insufficiency, its presence, nevertheless, does not rule out the diagnosis even of pure mitral stenosis. The diagnosis of a heart disease should be made not only from the findings of auscultation, but from the analysis of all data obtained on examination of the patient.

A mesodiastolic murmur, sometimes with a preceding additional heart sound (ventricular gallop rhythm) is a common sign of mitral insufficiency. The arising melogy is sometimes interpreted as a diastolic murmur of mitral stenosis with a preceding opening snap. In appraising the results of auscultation of the heart it must be borne in mind that a short diastolic murmur, whether isolated or with a preceding additional heart sound, is also among the signs of mitral insufficiency.

Enlargement of the left ventricle in a patient with mitral stenosis and with no signs of aortic valvular disease, arterial hypertension or rheumatic carditis testifies to the simultaneous existence of mitral insufficiency. In solving this problem, special significance should be attached to the results of echocardiography and electrocardiography. Right-ventricular hypertrophy and abnormal mobility of the valve cusps are typical of mitral stenosis. The appearance of signs of left-ventricular hypertrophy always points to the existence of one of the diseases listed above.

It is far more difficult to distinguish organic mitral insufficiency (congenital or rheumatic) from relative insufficiency which often appears in the clinical picture of aortic stenosis, arterial hypertension, systemic lupus erythematosus, cardiomyopathy, and atherosclerotic and myocarditic cardiosclerosis. The most reliable information is obtained in studying the peculiarities of the clinical course followed by these diseases.

Relative mitral insufficiency usually appears in the diseases listed in that period of their development when they are complicated by latent or obvious heart failure. In each case of this kind it is necessary to make a differential diagnosis between relative mitral insufficiency and an organic disease of this valve with predominant insufficiency.

Enlargement of the left atrium and signs of pulmonary hypertension are less pronounced in relative mitral insufficiency than in organic insufficiency of the valve. In organic mitral disease the murmur is usually harsh and pansystolic, in relative mitral insufficiency it has a blowing character and occupies only part of systole. Relative mitral insufficiency is mainly encountered in patients with drastic enlargement of all parts of the heart. Cor bovinum is not an obligatory sign of organic insufficiency of the mitral valve.

The gallop rhythm is a constant finding in relative mitral insufficiency, but a rare occurrence in organic insufficiency. The triple rhythm in relative mitral insufficiency is caused by the appearance of the third heart sound. In some cases, a short murmur is heard in the middle of diastole instead of the third sound. This mesodiastolic murmur is characterized by its variability. It disappears and reappears, now clearly heard, then hardly audible. In organic mitral insufficiency this murmur is very rare.

The findings of heart catheterization may be very valuable in making the differential diagnosis between organic and relative mitral insufficiency, but this manipulation is hardly applicable in a gravely ill patient with signs of severe circulatory failure. The results of treatment are usually of more substantial aid. The ventricular gallop rhythm and mesodiastolic murmur of relative mitral insufficiency disappear simultaneously with correction of the signs of circulatory failure.

In summing up all the abovestated it may be concluded that one should tend to make the diagnosis of severe rheumatic mitral insufficiency only when a pansystolic murmur and signs of congestive heart failure appear in the patient. In combination with the medical history and the type and time of the appearance of complications some other information of definite diagnostic value may be obtained.

Cardiac fibrillation develops in approximately one third of cases of organic mitral insufficiency. The incidence of this complication in relative mitral insufficiency is determined by the aetiology of the principal disease. It is a very rare complication of aortic stenosis but may be encountered in cardiomyopathy and atherosclerotic cardiosclerosis.

Congenital mitral insufficiency. The diagnosis of congenital mitral insufficiency is a very difficult problem. It is based on the combination of the characteristic clinical manifestations of the syndrome with the medical history and the results of heart catheterization. The final diagnosis is made during operation or on autopsy. Congenital mitral insufficiency is most commonly displayed by partial or complete splitting of the anterior cusp of the valve. Moreover, there are always some additional signs of anomalous development of the endocardial cushion. A particularly frequent

occurrence are accessory chordae tendineae arising from the interventricular septum (but not from the papillary muscles) and attached to the edges of the split cusp. These accessory chordae hold the halves of the split cusp and prevent their prolapse into the atrial cavity during systole.

When these anomalous chordae are too short, thick or fused, the mobility and function of the split parts of the anterior cusp are disturbed. It is important to bear in mind that an anatomically split anterior cusp of the mitral valve sometimes functions normally and does not lead to a complete picture of mitral insufficiency.

The abnormally formed anterior cusp of the mitral valve may be the only anomaly. It is the most common cause of congenital mitral insufficiency. There are other causes too: double mitral orifice with reduplication of the valve, congenital perforation of the cusp, shortening or absence of chordae tendineae and endocardial fibroelastosis.

The disease prevails among females. The symptoms may not be manifested for ten and sometimes even for twenty years. No symptoms with the exception of the mitral insufficiency murmur are found in this period of time. There are no complaints. Arrhythmias are the principal cause of deterioration in all cases. The older the patient, the more frequently disorders of rhythm occur; these are usually atrial arrhythmias. A murmur heard from childhood allows the diagnosis of congenital heart desease to be made. If one is unaware of this detail of the medical history, a diagnostic error may easily be made and the disease will be mistaken for the acquired form. The left-ventricular myocardium is strong and mitral insufficiency is therefore compensated for a lengthy period of time.

The systolic murmur is usually maximum at the apex beat and is often referred to the left and to the interscapular space. An apical pansystolic murmur is usually heard in combination with the third sound from which a short mesodiastolic murmur begins. Even if the sinus rhythm is preserved, atrioventricular conduction is prolonged as a rule. In two cases from our practice, cardiac fibrillation and atrial flutter developed after a lapse of twenty years. Wide, notched *P* waves were evidence of left atrial distension. Changes in the ventricular complex could be described as moderate to marked left axis deviation. The *R* waves were high in leads I and aVL and the *S* waves were deep in leads II, III and aVF. Both patients died from chronic heart failure.

Acute mitral insufficiency. Insufficiency of the mitral valve may occur suddenly, for instance in rupture of the left ventricular chordae tendineae or papillary muscles. In other cases acute mitral insufficiency may be a consequence of myocardial infarction with involvement of the papillary muscles, of papillary muscles malfunction, or may occur under the effect of injury. Two forms of acute

mitral insufficiency may therefore be distinguished: in some cases it occurs spontaneously and is as if an independent clinical condition; in others it develops in attendance to an already existing disease and is one of its complications.

We encountered spontaneous rupture of chordae tendineae only in males. In the literature we found a description of many cases of this malady among females. The disease usually begins with an attack of paroxysmal dyspnoea occurring either with no evident cause or in association with physical exertion. In one of our patients the attack of paroxysmal dyspnoea developed during an attempt to push his car which had stuck in the road. The attacks of paroxysmal dyspnoea are relatively mild in some cases or are attended by pulmonary oedema in others. Left-ventricular failure increases gradually, obliging the patient to seek medical aid.

The patients are usually middle-aged or elderly males who have no history of either rheumatic fever or heart disease. A harsh systolic murmur is heard on auscultation. The study of old case records proves that formerly this patient had no heart murmurs. A study of the medical history therefore helps to reveal an important differential diagnostic sign, namely, the recent appearance of the systolic murmur.

The other signs of acute mitral insufficiency are also attributed to the recent development of acute mitral insufficiency; they help in distinguishing it easily from the chronic form. A loud systolic murmur, severe shortness of breath and frequent attacks of paroxysmal dyspnoea appear in the late period of chronic mitral insufficiency, when the disease becomes decompensated. The left ventricle and the left atrium in this period of chronic mitral insufficiency are considerably enlarged. At the onset of acute mitral insufficiency they are normal in size. In later stages of the disease they become enlarged, but usually do not reach the dimensions found in chronic mitral insufficiency. Acute mitral insufficiency is easily distinguished from mitral stenosis by the absence of signs of pulmonary hypertension.

The sinus rhythm of the heart is maintained even in cases of acute mitral insufficiency with attendant signs of right-ventricular failure (hepatomegaly, oedema). Cardiac fibrillation developed in our patients at about the end of the first year after the disease had formed. Heart failure of approximately the same severity occurring in mitral stenosis and chronic mitral insufficiency is almost always complicated by cardiac fibrillation. The gallop rhythm in acute mitral insufficiency does not differ from that in chronic insufficiency.

In most cases, acute mitral insufficiency arises as a result of tearing of chordae tendineae holding the posterior cusp, and the systolic murmur of mitral insufficiency is therefore clearly transmitted to the base of the heart. Its remarkable similarity with the aortic

stenosis murmur is explained by the fact that it is attended by a thrill and is transmitted to the right subclavian and carotid arteries. A characteristic feature of this murmur is that it is louder over the right carotid artery than at the sternum in the right second intercostal space. It is generally known that the systolic murmur of aortic stenosis is always louder at the site where it is usually auscultated, than over the carotid arteries.

Moreover, the aortic stenosis systolic murmur is usually very clearly audible in the right second intercostal space whereas the maximum of the systolic murmur of mitral insufficiency is localized at the left sternal edge or over the heart apex and is clearly transmitted to the left axilla. Dilatation of the ascending aorta is a characteristic sign of aortic stenosis. It is not encountered in mitral insufficiency. In doubtful cases, a reliable diagnosis is made by catheterization of the left heart cavities. The considerable difference between pressure in the left ventricle and that in the aorta is evidence of aortic stenosis. Normal patency of the aortic orifice and the absence of a pressure gradient through the valve are typical of mitral insufficiency.

Echocardiography reveals disorders of normal mobility of the left ventricle and the left atrium. The remarkably high amplitude of the pulsation of their walls is a constant occurrence in acute mitral insufficiency, but is not characteristic of pronounced aortic stenosis. A freely moving posterior cusp of the mitral valve is sometimes discovered in the left atrial cavity.

Contrast ventriculography discloses mitral insufficiency but on no condition can it determine the cause. The same is true of the interpretation of the results of heart catheterization and of the results of its routine X-ray examination.

Spontaneous rupture of the mitral valve chordae tendineae is sometimes mistaken for myocardial infarction. An acute onset of the disease with an attack of paroxysmal dyspnoea and chest pains, recurrent attacks of paroxysmal dyspnoea and sometimes pulmonary oedema also are among the characteristic manifestations of myocardial infarction. The subsequent development of right-ventricular failure is always encountered in rupture of the chordae tendineae and is a frequent complication of myocardial infarction. The differential diagnosis between them presents no difficulties at the onset of the disease. The absence of characteristic ECG changes, the normal transaminase activity, the sudden appearance of the characteristic systolic murmur, and the absence of characteristic changes in the leucocyte count and ESR are testimony against myocardial infarction.

Gradual or at times rather rapid development of the clinical picture of mitral insufficiency is encountered in cardiomyopathy, both in the infiltrative and hypertrophic forms. Signs of mitral insufficiency developing in dermatomyositis and sarcoidosis disappear after steroid therapy.

Rupture of the chordae tendineae sometimes occurs as a complication of endocarditis lenta and rheumatic heart diseases. These complications may be suspected when (1) the course of the disease suddenly deteriorates, (2) the transmission of existing murmurs changes direction. In rupture of the chordae tendineae holding the anterior cusp the systolic murmur is referred to the left and to the interscapular space. In rupture of the chordae holding the posterior cusp the murmur is referred to the base of the heart.

Acute mitral insufficiency in myocardial infarction results either from rupture or from malfunction of the papillary muscles. The first of these complications is encountered no more frequently than in 1 per cent, and the second in about 30 per cent of cases of infarction. Both lead to the occurrence of the systolic murmur whose maximum is heard over the heart apex. The posterior papillary muscle is affected much more frequently than the anterior. It usually ruptures within the first week. Ruptures in later stages of the infarction are usually consequent upon a second infarction which had not produced a pain syndrome. The patients usually die in the first 24 hours after the rupture.

The chordae tendineae are torn away together with the heads of the papillary muscles in some cases or when the body of the muscle is ruptured in others. The diagnosis of the complication is based on the abrupt occurrence of pulmonary oedema to which shock develops in attendance soon afterward. When the papillary muscle ruptures suddenly the systolic murmur is never heard, evidently because auscultation of a patient with pulmonary oedema is difficult. When the complication develops slower or only the apex of one papillary muscle is torn off, a harsh systolic murmur is auscultated for two or three days.

Acute mitral insufficiency occurring as a consequence of infarction of the papillary muscles must be differentiated from ventricular septal rupture which is encountered in approximately 0.5 per cent of cases of myocardial infarction. It occurs in the same terms as rupture of the papillary muscles, i.e. in the period of the maximum degree of myomalacia. Rupture of the interventricular septum usually occurs with intolerable pains in the region of the heart. At the moment of rupture the patient faints, after which the picture of shock develops. In most cases the rupture occurs in the muscular part of the septum, closer to the apex of the heart.

A harsh systolic murmur appears in the precordial region and a systolic thrill is felt. Quite often the systolic murmur is clearly transmitted to the heart apex, but the zone of its maximum loudness is usually the third to fifth intercostal space to the left of the sternum. It is clearly auscultated in the interscapular space and is transmitted to the left axilla and to the right of the sternum up to the anterior axillary line.

If the patient survives the moment of the rupture, sharp pain in the right hypochondrium appears first because of the rapid swelling of the liver. Signs of right-ventricular failure advance with every day and right axis deviation is recorded on the ECG.

The combination of shock with acute left-ventricular failure is encountered quite often also in extensive myocardial infarction with involvement of the papillary muscles but without their rupturing. The causes for the progressive growth of pulmonary oedema in these heart diseases should evidently be attributed to sharply developing insufficiency of the mitral valve and simultaneous functional insufficiency of the left-ventricular myocardium. The picture of acute left-ventricular failure in rupture or severe lesion of the papillary muscles serves as a background against which another also constant syndrome suddenly occurs, namely shock. Rupture of the ventricular septum is marked by diminished signs of left-ventricular failure and progressive growth of the signs of right-ventricular failure.

Thus, acute mitral insufficiency developing in conjunction with myocardial infarction differs from infarction with ventricular septal ruptures mainly in its course. Left-ventricular failure predominates in the clinical picture of myocardial infarction with acute mitral insufficiency. The replacement of the picture of left-ventricular failure by that of right-ventricular failure suggests rupture of the interventricular septum. This change and not the character and irradiation of the auscultated systolic murmur should be accepted as the principal differential diagnostic criterion.

Aortic Stenosis

The diagnosis of aortic stenosis is based on the characteristic systolic murmur which, in combination with the medical history and signs detected by physical examination, makes it possible to judge the aetiology and severity of the syndrome.

Heart failure is a frequent complication of aortic stenosis and one of the factors making the disease a diagnostic problem. It usually begins either with gradually increasing shortness of breath on physical exertion, or with attacks of paroxysmal dyspnoea. A pronounced clinical picture of right-ventricular failure with hepatomegaly, oedema, and ascites is only encountered in aortic stenosis in the elderly and old patients. Death of young patients occurs suddenly, usually before the picture of right-ventricular failure develops. The severer the heart failure, the more often patients with aortic stenosis have attacks of restlessness, profuse sweating and marked hypotension. Death usually occurs during a collapse which is sometimes mistaken for a manifestation of myocardial infarction.

In individuals under 30 years of age, aortic stenosis is induced as a rule by a calcified unicuspid valve. The calcification of a bicuspid valve usually occurs between the ages of 30 and 40. Isolated aortic stenosis of old age most frequently develops in males and is one of the manifestations of Moenckeberg's arteriosclerosis of the aorta. Some authors claim that an isolated rheumatic aortic stenosis is a very rare occurrence, whereas others contend that it is not encountered at all.

Stenosis of the aortic orifice occurs relatively quickly in some cases and very slowly in others. Early formation of the stenosis is generally attributed to the effect of haemodynamic factors, whereas its formation only between the ages of 70 and 90, to degenerative changes in the aortic ring and cusps. The first complaints appear when the area of the aortic orifice is reduced to 1 cm^2. The classical signs of the disease are found when the area reduces to 0.6 cm^2.

Fatiguability and shortness of breath are among the earliest complaints made by a patient with aortic stenosis. They appear on physical exertion and do not abate for a great length of time restricting the patient's working capacity. Somewhat later physical exertion becomes attended by dizziness. Marked aortic stenosis has the following characteristic triad of signs: syncope, attacks of angina pectoris and attacks of paroxysmal dyspnoea.

In milder cases of aortic stenosis, physical exercise causes dimness of vision, whereas in severer cases the patient loses consciousness. Syncope occurs during, or soon after, physical exercise. The load of physical exertion inducing syncope is in direct proportion to the severity of aortic stenosis. Syncope and dimmed consciousness occurring during an attack of paroxysmal dyspnoea and pulmonary oedema are particularly menacing as regards prognosis.

Syncope is explained in some cases by the inability of the left ventricle to increase its debit so as to meet the physical exertion, and in others by the concomitant disorders of heart excitability and conduction. In some cases of aortic stenosis, simultaneous calcification of the aortic valve cusps and fibrous ring develops. This is clinically manifested either by impaired atrioventricular conduction or by bundle branch block. Disorder of conduction sometimes develops long before calcification of the valve. Total atrioventricular block makes it difficult to recognize aortic stenosis. Syncope in these patients is often mistaken for a manifestation of heart block and not of aortic stenosis.

Pain in the heart is among the most common symptoms of aortic stenosis. In the early stages of the disease it is of the type of cardialgia. A typical angina pectoris syndrome develops in approximately two thirds of cases of severe aortic stenosis. The character, cause, localization and radiation of pain do not differ from identical pain

in atherosclerosis of the coronary arteries. It does not proceed from the abovestated, however, that the absence of angina pectoris is evidence of a mild stenosis. In our experience there were patients in whom severe right-ventricular failure was the first complication of aortic stenosis. After heart failure develops, the attacks of angina pectoris often disappear, but sometimes they become more severe.

The appearance of angina pectoris, syncope and left-ventricular failure is the turning point in the patient's fate. About 80 per cent of patients with aortic stenosis die within four years after the occurrence of the clearly demonstrated triad or of one of its components. In approximately 5 per cent of cases, death occurs suddenly.

Aortic stenosis may often be diagnosed on the basis of a carefully taken medical history. The size of the left ventricle is particularly important in making the diagnosis and appraising the severity of aortic stenosis. Left-ventricular hypertrophy may be confidently revealed by palpation. An intensified apex beat sometimes appears before signs of left-ventricular hypertrophy are recorded on the ECG. Presystolic pulsation of the left atrium as well as the electrocardiographic signs of its hypertrophy are among the most reliable diagnostic criteria of aortic stenosis, but only in patients who reveal no signs of left-ventricular failure. In a patient with left-ventricular failure these signs appear in atherosclerotic cardiosclerosis, in aortic insufficiency, in mitral insufficiency and, sometimes, in cardiomyopathy.

All young and middle-aged patients with aortic stenosis have a sinus heart rhythm. The appearance of cardiac fibrillation always testifies to concomitant mitral stenosis. Aortic stenosis in patients of old age is complicated in rare cases by cardiac fibrillation which may be a consequence of concomitant atherosclerotic cardiosclerosis. In our experience, the sinus rhythm was maintained even in severe circulatory failure only in cases of isolated aortic stenosis. In all other cases, severe circulatory failure in aortic-mitral heart diseases developed in the presence of cardiac fibrillation. Unfortunately, this fact has not been sufficiently reflected in the Soviet literature and its wrong interpretation is one of the causes of an erroneous diagnosis of mitral insufficiency in patients with isolated aortic stenosis.

The characteristic systolic murmur is of high diagnostic significance but it is sometimes inaudible in severe heart failure and in old persons with an emphysematous chest. The musical character of the systolic murmur is usually encountered in patients old in age. It bears no relation to the severity of the stenosis. It is easily seen on the phonocardiogram that the maximum amplitude of this murmur is usually in the first half of systole; the further it is from the beginning of the first sound, the severer the stenosis. Paroxysmal

splitting of the second sound in patients with no sings of impaired intraventricular conduction is only encountered in severe aortic stenosis.

Arterial pressure is usually normal in aortic stenosis. High pulse pressure is explained by systolic hypertension usually developing in patients of old age. Normal arterial pressure does not rule out pronounced aortic stenosis. Low pulse pressure, e.g. below 30 mm Hg, is always evidence of severe aortic stenosis. Marked diastolic hypertension is often encountered in aortic stenosis in aged persons with signs of heart failure.

Calcification of the aortic valve is a reliable diagnostic sign of aortic stenosis. It is commonly encountered in all males older than 35 and in all females older than 45.

However great the diagnostic significance of hypertrophy of the left ventricle may be, in many cases of mild aortic stenosis its size is nevertheless normal. An enlarged left ventricle in aortic stenosis is most common in patients with heart failure or in patients with a history of heart failure. Both the left ventricle and the left atrium are enlarged. In appraising the results of X-ray it must be borne in mind that the left atrium is enlarged before signs of heart failure appear. With the gradual formation of aortic stenosis pressure in the left ventricle gradually increases and the working load experienced by the left atrium grows. The functioning of the left atrium under increased pressure leads to its hypertrophy and to dilatation in the long run. The higher the diastolic pressure in the left ventricle, the more clearly the electrocardiographic and X-ray signs of left atrial hypertrophy and dilatation are demonstrated.

Enlargement of the left atrium is encountered almost in all cases of rheumatic mitral diseases, but one should not forget that this regularity does not allow a reverse conclusion, in other words it does not provide grounds to consider that enlargement of the left atrium always indicates the presence of rheumatic mitral disease in the patient.

Erroneous interpretation of the systolic murmur of aortic stenosis is yet another reason for hyperdiagnosis of concomitant mitral disease. This murmur is sometimes heard only over the heart apex and in such instances it is mistaken for a murmur caused by mitral insufficiency or even mitral stenosis.

The difficulties of differential diagnosis will become all the more obvious if it is taken into account that cases of mild aortic stenosis may produce no X-ray or electrocardiographic signs of left-ventricular hypertrophy. The diagnosis of aortic stenosis is very convincing when signs of aortic valve calcification are found. Catheterization of the heart cavities is resorted to in diagnostically doubtful cases.

In some instances, the auscultative findings do not provide a

basis for distinguishing aortic stenosis from mitral insufficiency. Phonocardiography helps to identify the true cause of the systolic murmur. Aortic stenosis is distinguished by the diamond shape of the systolic murmur and diminution of the aortic component of the second sound, which is detected more clearly by simultaneous recording of the carotid artery pulse. The site of the origin of the murmur is differentiated well on an intraoesophageal or intracardiac phonogram.

The blood pressure difference across the aortic valve is of decisive significance when aortic stenosis is suspected. Unfortunately, heart catheterization, which alone can reveal this sign, is rarely performed in the hospital for internal diseases either because the patient's condition is grave or because there is no special equipment. That is why aortic stenosis is diagnosed less frequently than it is encountered. In our practice we had never a case of the hyperdiagnosis of aortic stenosis, but its signs and complications were mistaken again and again for signs and complications of some other disease.

When the methods of examination mentioned above cannot be conducted for this or that reason, particular attention is focused at the results of X-ray examination. A considerably enlarged left atrium is only encountered in mitral insufficiency, whereas dilatation of the ascending aorta is found only in aortic stenosis. The gallop rhythm with a mesodiastolic murmur is only heard in mitral insufficiency.

The results of echocardiography are particularly important in making the differential diagnosis. Characteristic distension of the aortic root and the type of its movement during systole are recorded on the echocardiograms. The movement of the right coronary (anterior) and non-coronary (posterior) cusps of the aortic valve can sometimes be traced (Gibson, 1973). Moreover, the character of mitral valve movements during diastole makes identification of mitral stenosis, both the aphonic form and the form marked by one systolic murmur, easier.

Of no less differential diagnostic significance are the signs of pulmonary hypertension which is usually found only in cases of mitral stenosis. In aortic stenosis, signs of interstitial pulmonary oedema are encountered only in patients with a drastically enlarged left ventricle, whereas in concomitant mitral stenosis they may be clearly demonstrated even in patients with normal heart dimensions.

Signs of aortic insufficiency are found in approximately 20-30 per cent of patients with congenital aortic stenosis. The diastolic murmur in such cases has a typical diminishing character and is usually best heard in the third intercostal space on the left, close to the sternum. This is a weak murmur as a rule and it is detected

only by very attentive auscultation. Aortic insufficiency is found in approximately two thirds of cases with aortic stenosis of sclerotic origin. The clinical picture and the course of the disease are always determined by aortic stenosis, while insufficiency of the aortic valve is a concomitant lesion.

Atherosclerosis of the aorta and particularly *syphilitic aortitis* frequently lead not only to distension of the ascending aorta but also to the appearance of a systolic murmur of relative stenosis of the aorta. In most cases this murmur is weak and short. It occupies only part of systole and is not intensified in the middle of systole. The second heart sound over the aorta far from being diminished often becomes louder.

A prolonged systolic murmur of *ventricular septal defect*, like the murmur of aortic stenosis, intensifies noticeably at the end of systole. A systolic thrill is detected simultaneously with the murmur in about two thirds of cases. When the diameter of the defect is small, the systolic murmur is heard only at the beginning of systole. In the midsystole the defect closes and the flow of blood from the left into the right ventricle ceases. The intensity of the murmur points to its organic origin. The dimensions of the heart do no change in such cases. A pansystolic murmur indicates that the shunt of blood into the right ventricle continues during entire systole. It is best heard in the third, fourth and sometimes also in the fifth intercostal space at the left sternal edge. It is clearly transmitted to the right and left. There is splitting of the second sound, but it is not fixed. The distance between the second sound components on inspiration and expiration does not change. A prolonged systolic and a short diastolic murmurs are heard in cases with a large ventricular septal defect. The left ventricle is commonly enlarged and sometimes the left atrium is likewise enlarged. Signs of pulmonary hypertension are found in the patient and cyanosis appears from time to time. Signs of biventricular hypertrophy are recorded on the electrocardiogram and radiographs when pulmonary hypertension is pronounced.

Aortic stenosis differs from ventricular septal defect in the localization and distribution of the systolic murmur. Signs of calcification are discovered only in aortic stenosis; diffuse cyanosis develops only in a case of ventricular septal defect. The signs listed are found in far advanced cases of the disease. Catheterization of the heart has to be undertaken for making a precise diagnosis in milder cases.

The systolic murmur of aortic stenosis often has to be differentiated from a murmur occurring in *stenosis of the pulmonary artery*. It is generally accepted that the aortic stenosis murmur is best heard in the second right intercostal space and the murmur of pulmonary artery stenosis in the second left intercostal space. This

diagnostic criteria, however, cannot be considered reliable. It is easier to distinguish these diseases by the results of X-ray and electrocardiography. Post-stenotic dilatation of the aorta is found in one case and of the pulmonary artery in the other.

Aortic stenosis is manifested on the ECG by signs of left-ventricular hypertrophy. In stenosis of the pulmonary artery, signs of right-ventricular hypertrophy are demonstrated. The differential diagnosis between these two diseases can usually be made without resorting to special studies of haemodynamics.

The systolic murmur in *stenosis of the aortic isthmus* (coarctation of the aorta), like the murmur of aortic stenosis, is best heard over the base of the heart. Arterial blood pressure in coarctation of the aorta, as in aortic stenosis, is normal or elevated. Coarctation of the aorta is easily differentiated from aortic stenosis if the rule is observed to examine the femoral artery pulse in every patient. A sharply weakened and delayed pulse in the femoral artery is characteristic of coarctation of the aorta. In aortic stenosis the femoral artery pulse is usually of a somewhat higher amplitude than the pulse in the radial artery. Blood pressure in the brachial arteries is always higher than blood pressure in the femoral arteries. In aortic stenosis and in healthy persons blood pressure is always lower in the brachial arteries than in the femoral arteries.

A high position of the arch of the aorta, intensified pulsation of the carotids which is clearly visible by the naked eye, and signs of extraordinarily developed collateral arterial circulation (subcutaneous pulsation of the intercostal arteries and lateral thoracic arteries, indentations on the lower rib edges) are often encountered in coarctation of the aorta and are not typical of aortic stenosis.

In patients with aortic stenosis, arterial pressure is often elevated and may sometimes exceed 200 mm Hg (systolic) and 100 mm Hg (diastolic). It rises particularly in attacks of acute left-ventricular failure. If we recall that aortic stenosis is often marked by attacks of pain in the heart, the reason for the frequent need to rule out myocardial infarction in these patients will become immediately clear. Not only these clinical data but also the results of electrocardiography make one suspect that the patient has myocardial infarction. Besides deflection of the *S-T* segment and flattening or even inversion of the *T* wave, these patients often have deep *Q* waves in leads I, aVL, V_5 and V_6. In a young patient these abnormalities on the ECG occur in association with drastic hypertrophy of the interventricular septum. When the syndrome mentioned above (chest pain, anginal attacks, ECG abnormalities) is found in an elderly patient, one suspects above all else that the patient is suffering from infarction of the left-ventricular anterolateral wall.

In most of our cases of aortic stenosis, microfocal necroses were found which were localized in the subendocardial coat of the left

ventricle. A series of ECG recorded dynamic changes in the *ST-T* complex in these cases. Extensive fresh infarcts and extensive cicatricial fields consequent upon earlier infarctions were rare. In making the diagnosis of myocardial infarction in such cases, one should attach special importance to the results of repeated tests for aminotransferase activity, the appearance of areas of left-ventricular dyskinesia and akinesia on the echocardiogram and disorders of cardiac rhythm. The last sign acquires particularly high diagnostic significance if it occurs after attacks of pain or coincides in time with a sudden deterioration in the patient's condition (the diagnosis of myocardial infarction is discussed in detail in the chapter 'Chest Pain').

A harsh systolic murmur over the base of the heart attended by a thrill is a constant sign of *acute mitral insufficiency* occurring as a consequence of rupture of the left-ventricular chordae tendineae. Its differential diagnosis from aortic stenosis is described in the section 'Mitral Insufficiency'. Besides the described stenosis of the aorta at the level of the valve ring, supravalvular and subvalvular (subaortic) aortic stenoses are distinguished. A subvalvular aortic stenosis may be organic or functional. The most common cause of organic stenosis is a fibrous tissue membrane separating the left ventricle into two. A bicavitary left ventricle (membranous type) occurs. In some cases a drastically hypertrophied upper part of the ventricular septum constricts the outflow tract from the left ventricle transforming it into a narrow tunnel (the tunnel type). This stenosis is purely functional. It occurs only during a left-ventricular systole and disappears completely during its diastole.

Hypertrophic subaortic stenosis has commonly to be distinguished from valvular aortic stenosis. The first signs of hypertrophic subaortic stenosis usually appear between the ages of 20 and 40. The patient does not make any complaints as yet, but a systolic murmur, moderate left-ventricular hypertrophy and abnormalities on the ECG are found on chance examination. Complaints of pain in the heart and shortness of breath even in normal physical exertion appear several years later.

The systolic murmur begins with a slight digression from the first sound, it is diamond-shaped and clearly transmitted along the left sternal edge to the apex and less clearly to the neck vessels. We failed to distinguish it from the systolic murmur of moderate valvular aortic stenosis either by auscultation or by the phonocardiogram. More reliably these diseases are distinguished by the presence (valvular stenosis) or absence (hypertrophic subaortic stenosis) of pronounced post-stenotic dilatation of the ascending aorta and deposits of calcium salts in the aortic valve. The ejection sound is hardly ever encountered in subaortic stenosis, but is a fre-

quent sign of aortic valvular stenosis. The fourth heart sound is recorded in about 50 per cent of patients with hypertrophic subaortic stenosis and no signs of heart failure. It is a rare finding in valvular aortic stenosis. The ascending limb of the pulse wave rises slowly in valvular aortic stenosis and more rapidly than normal in subvalvular stenosis.

A usually weak diastolic murmur of aortic insufficiency is often heard in severe valvular aortic stenosis. Hypertrophic subaortic stenosis is never complicated by aortic insufficiency. Cardiac fibrillation is known to be the most common cause of subaortic stenosis decompensation. In valvular aortic stenosis, the heart still beats in a sinus rhythm even after the development of hepatomegaly, anasarca and ascites.

Hypertrophy of the upper part of the interventricular septum is displayed on the ECG by deep *Q* waves usually in leads II, III and aVF, but is best detected on the ventriculograms and the echocardiograms. The thickness of the interventricular septum exceeds 1.5 cm in hypertrophic subaortic stenosis. It is no less than 1.5 times thicker than the hypertrophied posterior wall of the left ventricle. The transverse diameters of the posterior left-ventricular wall and the interventricular septum are sharply increased in valvular aortic stenosis, but always in direct proportion to each other. In valvular aortic stenosis the thickness of the interventricular septum exceeds the thickness of the posterior left-ventricular wall by 1.1 times, on the average.

Other echocardiographic signs of hypertrophic subaortic stenosis are of definite diagnostic value. These are diminished amplitude of movements of the interventricular septum, altered character of movements of the anterior aortic valve cusp, and anomalous mobility of the anterior mitral valve cusp which hits the interventricular septum at the moment of maximum opening. With the development of heart failure these signs become less manifest and may completely disappear. If it is remembered that adequate echocardiograms cannot be recorded in every patient and that the thickness not of the entire interventricular septum but only of its upper part is recorded on the echocardiogram the need to resort, in some cases, to bilateral ventriculography becomes obvious.

The interventricular septum of the heart of a healthy person bulges slightly into the right ventricle and both its surfaces are always parallel to each other. In hypertrophic subaortic stenosis the upper part of the septum thickens earlier and more sharply than the lower part. As a result the septum is seen as a triangle on movie-camera frames and its left-ventricular and right-ventricular surfaces diverge and are no longer parallel to each other. The septal surface in the left ventricle may be straight or bulging into its cavity. Its surface in the right ventricle remains slightly protruding.

Errors in the diagnosis of aortic stenosis are usually due to inaccurate identification of the systolic murmur characteristic of this disease. In heart failure, the intensity of this sound sharply diminishes and it is not infrequently mistaken for the murmur of rela-

tive aortic stenosis. Practitioners are still insufficiently informed about the possible elevation of arterial pressure in aortic stenosis. As a result of this some cases of aortic stenosis are mistaken for hypertensive disease. Aortic stenosis is commonly attended by insufficiency of the aortic valve, relative mitral insufficiency, and relative coronary insufficiency with subendocardial myocardial necroses. The diflerential diagnosis of these complications should be made with especial care.

Aortic Insufficiency

The aetiology of aortic insufficiency is the principal factor determining the rate of its irresistible progressive course. Drug therapy may slow down the progression of some types of aortic insufficiency, thus preserving the patient's life and prolonging his working capacity. A similar result may be achieved in some cases by timely valve prosthetics. These advances in surgery and in the nonoperative management of internal diseases provide grounds for the assumption that in our time the diagnosis of aortic insufficiency, the proper assessment of its severity, and identification of its cause have extended beyond the limits of academic interest, acquiring practical significance.

Chronic aortic insufficiency. Aortic insufficiency is caused either by deformity of the valve cusp or by dilatation of the root of the aorta (see the section 'Diastolic Murmur'). Both types of the disease may occur under the effect of one and the same cause. It is therefore expedient to distinguish the types of aortic insufficiency according to the aetiological principle. In adherence to this principle (see Supplement XIV-1), *congenital and acquired* aortic insufficiency may be distinguished.

Detailed questioning of the patient about the beginning and character of the course of the disease noticeably helps to identify the cause of aortic insufficiency. Acute polyarthritis suffered in childhood provides grounds for presuming its rheumatic origin. This presumption is given even more substantiation if it is found out that the patient had suffered recurrences of polyarthritis. Absence of a history of acute polyarthritis does not exclude the rheumatic origin of aortic insufficiency, because cardiac forms of rheumatic infection are often unattended by involvement of the joints.

Considerable significance should be attached to the information about the age at which the diagnosis of aortic insufficiency had been made for the first time. Its congenital origin is assumed if it was first discovered in early infancy. The association of aortic insufficiency with rheumatic infection is highly probable if the diastolic murmur was detected for the first time in childhood or adoles-

cence. The appearance of aortic insufficiency after 30 years of age provides grounds for suspecting its syphilitic origin. Other diseases which may be complicated by aortic insufficiency in the middle-aged or elderly are dissecting aneurysm of the aorta, aneurysm of Valsalva's sinus, calcification of the aortic valve, and diffuse connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, scleroderma).

Verrucous endocarditis of the aortic valve in systemic lupus erythematosus was described as early as at the turn of the century. Aortic insufficiency is very rare in this disease like in spondyloarthritis and Reiter's syndrome. Heart failure is often diagnosed in scleroderma, but in very rare cases of this disease it is induced by a disease of the aortic valve.

Aortic insufficiency in rheumatoid arthritis is caused by granulomatous lesions of the aortic valve whose cusps are first thickened and then shortened due to connective tissue cicatrization. The ascending aorta is sometimes also involved. Calcium salts may be deposited in the foci of inflammation in which case calcified foci in the aorta and valve are demonstrated by X-ray (as in syphilis).

Aortic insufficiency sometimes develops in a person who seems to be in sound health. A diastolic murmur appears with no evident cause and is transmitted along the right sternal edge. The systolic arterial pressure is slightly elevated, the diastolic pressure remains normal. X-ray shows dilatation of the ascending aorta. The Treponema pallidum immobilization test is negative and the cause of aortic insufficiency remains unrecognized. Patients die from heart failure. Aortitis or necrosis of the aortic media is discovered on autopsy.

In some cases of aortic insufficiency the large arteries arising from the arch of the aorta are involved simultaneously with the aorta. The principal syndrome of the disease is arterial hypertension, as a rule, the differential diagnosis of which is discussed in a special section.

The diastolic murmur of relative aortic insufficiency is sometimes encountered in thyrotoxicosis, anaemia, uraemia and severe arterial hypertension. It disappears when the signs of these syndromes are corrected.

In old age, aortic insufficiency is only mildly pronounced and usually occurs in conjunction with aortic stenosis. Dilatation of the aortic root is its morphological underlying factor. Simultaneous dilatation of the ascending aorta is often encountered. The pulse arterial pressure is mildly elevated, the diastolic pressure never drops to very low values.

Aortic insufficiency may be induced by bacterial endocarditis at any age. It is characterized by rapid development of severe aortic

insufficiency against the background of a more or less protracted febrile disease.

The aetiology of aortic insufficiency may be identified in some cases by the findings of physical examination. It may be assumed that aortic insufficiency in a patient with blue sclerae is most likely one of the signs of osteogenesis imperfecta, whereas in a patient with rheumatoid arthritis or Marfan's syndrome it is a sign of these diseases. Destruction of the cartilaginous part of the nose and ears is testimony of recurrent polychondritis in whose clinical picture the syndrome of aortic insufficiency is a component.

An Argyll Robertson pupil, absence of the pupillary reaction to light, absence of tendon reflexes, and the presence of other signs of a lesion of the central nervous system commonly occurring in combination with a positive Wassermann reaction provide grounds for assuming the association of aortic insufficiency with syphilis.

Splenomegaly, proteinuria, microhaematuria and protracted fever oblige the physician to search for other signs of bacterial endocarditis. Simultaneous affection of several body systems suggests that aortic insufficiency is a consequence of Libman-Sacks endocarditis.

The combination of aortic valve insufficiency with aortic stenosis at young age is only encountered in rheumatic fever. Their combination in elderly and old patients is frequently associated with calcinosis of the aortic valve.

The results of electrocardiography are of no decisive importance in the diagnosis of aortic insufficiency. In mild cases the ECG may show no changes. In severer cases signs of left-ventricular hypertrophy are recorded. If in a patient with diastolic murmur right axis deviation and signs of right-ventricular hypertrophy are recorded, then this diastolic murmur should be interpreted as the murmur of mitral stenosis and not as Flint's murmur.

X-ray reveals no noticeable changes in the heart in mild aortic insufficiency. In cases of greater severity a characteristic X-ray heart outline with an emphasized waist and enlarged left ventricle appears. Calcification of the ascending aorta and Valsalva's sinus, particularly in the middle-aged, provides grounds for presuming that aortic insufficiency is of syphilitic origin. Calcinosis of the aortic valve is usually encountered in aortic stenosis. The signs of aortic insufficiency in such cases are mild as a rule.

In summarizing all that is discussed above it may be stated that in approximately 90 per cent of cases aortic insufficiency arises due to the effect of the 'big four' factors: rheumatic fever, bacterial endocarditis, syphilis and aortic valve calcification. Only 10 per cent of cases falls to the share of the other causes listed in Supplement XIV-2.

Rheumatic fever is the most common cause of aortic insufficien-

cy. It accounts for about 70-80 per cent of all cases with this syndrome. This justifies our discussion in such great detail of the regular pattern of the clinical course and the peculiarities of the diagnosis of rheumatic aortic insufficiency.

Aortic insufficiency of rheumatic origin is encountered much more frequently among males than among females. The diastolic murmur usually appears soon after an attack of rheumatic fever. In most cases a marked clinical picture of aortic insufficiency develops seven to ten years after the appearance of this murmur. In the following ten years the patient's condition remains quite satisfactory. Physical examination reveals an intensified apex beat and a rounded apex of the left ventricle. The patients continue to feel well also when the heart is moderately enlarged.

Progressive deterioration begins with the appearance of pains and palpitation. At first they are experienced only during abnormal physical exertion. Later, they begin appearing at night. By this time the heart is considerably enlarged and signs of left-ventricular overstress are seen on the electrocardiogram. Two thirds of the patients with the left-ventricular overstress syndrome die within three years. With the appearance of left-ventricular failure the prognosis becomes especially severe.

Hypertensive crises, attacks of tachycardia, and profuse sweating are encountered in the gravest cases of aortic insufficiency. Patients suffer from nightmares and abdominal pains the intensity and localization of which correspond to those of pains in pancreatitis, gastric ulcer or acute cholecystitis. In about 25 per cent of patients aortic insufficiency is complicated by bacterial endocarditis.

The severity of aortic insufficiency should be appraised according to the size of the heart, clarity of the third heart sound, abnormalities recorded on the ECG, and the duration of the diastolic murmur. The loudness of the murmur and the degree of the peripheral signs of aortic insufficiency have neither diagnostic nor prognostic significance. The life prognosis becomes very serious after signs of right-ventricular insufficiency appear.

The diagnosis of isolated aortic insufficiency may be established in most cases at the patient's bedside without resorting to any additional methods of examination. It is far more difficult to make the diagnosis when this disease is combined with mitral stenosis or with aortic stenosis, i.e. in most cases of rheumatic fever.

The possibility of aortic insufficiency as a concomitant disease should be borne in mind in all cases of mitral stenosis in which electrocardiographic and X-ray signs of left-ventricular hypertrophy are found. Moderate dilatation of the ascending aorta is also evidence of concomitant aortic insufficiency because such dilatation is never encountered in isolated mitral stenosis. The pulse arterial pressure is always below normal in mitral stenosis and its elevation

is therefore detected only in patients with mitral stenosis and concomitant aortic insufficiency.

Sudden elevation of arterial pressure sometimes leads to the appearance of prolonged diastolic murmur which is clearly audible in the second right intercostal space and in Botkin's point. With a drop in arterial pressure to normal level the auscultative signs of aortic insufficiency disappear. We encountered temporary aortic insufficiency as a regular pattern in elderly patients and patients in old age suffering from hypertensive disease. The murmur is evidently caused by stretching of the aortic valve ring under the effect of sharp elevations of arterial pressure.

Insufficiency of the aortic valve of rheumatic origin is often a component of a more complex heart affection. It is encountered particularly often simultaneously with stenosis of the mitral orifice and with aortic stenosis. The physical and haemodynamic signs of aortic insufficiency in such cases are less manifest. When signs of aortic stenosis develop in attendance to aortic insufficiency, the systolic arterial pressure drops below normal level, while the diastolic pressure in the left ventricle rises above normal. This results in a decrease in pulse pressure which is inherently a hazard of the underestimation of the severity of the heart disease. The diastolic murmur becomes diminished and only the electrocardiographic signs of left-ventricular hypertrophy indicate that this weak murmur obscures severe aortic insufficiency.

Aortic insufficiency of syphilitic origin has been encountered much more rarely in recent years than formerly. The aorta may sometimes be already affected in secondary syphilis, but relative aortic insufficiency causes no functional disorders of the cardiovascular system for six to ten years. Before World War II the survival period from the time of the establishment of the diagnosis of syphilitic aortic insufficiency was one and a half to two years, on the average. Today, due to the advances in treatment, 43 per cent of these patients have a survival period of over 10 years and 30 per cent—a survival period of over 15 years from the time the diagnosis of aortic insufficiency is established.

The diastolic murmur in syphilitic aortic insufficiency is often of a musical character. It is transmitted along the right sternal edge, as a rule. Angina pectoris in syphilitic aortitis is distinguished by resistance to the usual therapeutic methods and is often combined with left-ventricular failure. Calcinosis of the ascending aorta is encountered at about 40 years of age in syphilitic aortitis and usually after the age of 60 in atherosclerosis. A positive Treponema pallidum immobilization test allows the aortic insufficiency revealed in the patient to be attributed to syphilis.

Aortic insufficiency in acute bacterial endocarditis is usually associated with anatomic destruction of the valve cusps. It is not the

predominant syndrome of bacterial endocarditis and does not determine the outcome of the disease. It is extremely difficult to make its diagnosis in acute sepsis because of the patient's grave general condition and such complications of sepsis as pneumonia, pericarditis, meningitis and peritonitis.

Aortic insufficiency in endocarditis lenta develops less acutely as a consequence of which it is mostly diagnosed during life. The diastolic murmur in this form of aortic insufficiency often has a musical character. Its appearance is linked with perforation of the aortic valve cusps. As a result of drastic destruction of the valve, the peripheral signs of aortic insufficiency are usually manifested far more sharply in endocarditis lenta than in rheumatic fever or syphilis.

Congenital aortic insufficiency is encountered as an isolated defect of the valve cusps (their fenestration, myxoedematous degeneration, bicuspid or quadricuspid valves) or in combination with other developmental defects of the aorta. Aortic insufficiency is a frequent occurrence in Marfan's syndrome, aneurysm of Valsalva's sinus, ventricular septal defect, and coarctation of the aorta.

A bicuspid valve functions normally till it undergoes calcification. That is why neither a diastolic nor a systolic murmur is usually auscultated in childhood in a patient with a bicuspid valve. These murmurs appear later when the valve cusps lose their normal activity because of calcium deposits. A bicuspid valve is found in 25 to 50 per cent of cases of aortic coarctation. It is often the site of the development of microbial colonies in bacterial endocarditis.

Aortic insufficiency is encountered approximately in 6 per cent of cases of ventricular septal defect. Only a systolic murmur is heard at birth. The diastolic murmur of aortic insufficiency appears later, usually between the ages of eight and ten. The exact diagnosis of the disease is established only after angiocardiography.

Aortic insufficiency of iatrogenic origin has been encountered in recent years. It should be expected that the incidence of this type of aortic insufficiency will grow with time. Two types of iatrogenic aortic insufficiency are distinguished: in some cases it develops after aortic valvulotomy, in others it occurs after aortic valve prosthetics.

Aortic insufficiency consequent upon aortic valvulotomy is almost always mild. The soft diastolic murmur is transmitted as usual, i.e. it is best heard in the third intercostal space at the left sternal edge. Aortic insufficiency may occur immediately or soon after the application of a prosthesis the diameter of which proves to be larger than optimum. In such cases the aortic wall begins to bulge into the frame of the prosthesis preventing the ball from returning snugly to its initial place during diastole. The signs of aortic insufficiency may appear a few weeks after surgery. Signs of bacte-

rial endocarditis develop simultaneously with aortic insufficiency in such cases.

In the late postoperative periods, aortic insufficiency is usually caused by degeneration of the prosthesis. Sometimes the cause of aortic insufficiency is a false passage formed between the aortic wall and the outer surface of the prosthesis. In such instances the blood flows during diastole along this passage from the aorta into the left ventricle by-passing the prosthesis.

Weakening of one or both characteristic clicks of the artificial valves is the first sign of these complications. The signs of aortic insufficiency appear later, usually simultaneously with thromboembolisms in the arteries of the systemic circulation. Embolism of the aortic bifurcation is a particularly frequent occurrence. The source of the embolisms are thrombi on the surface of the degenerated aortic prosthesis.

Acute aortic insufficiency sometimes occurs after a *closed chest injury*. Rupture of one of the valve cusps takes place more often, while separation of the commissures happens less frequently. Other signs of injury to the heart, disorders of conduction, and accumulation of fluid in the pericardial cavity appear simultaneously with aortic insufficiency.

Traumatic aortic insufficiency is always severe. Its peripheral signs are constantly sharply manifested. The diastolic murmur resulting from vibration of the valve cusps in the blood stream is always very loud and often heard at some distance from the patient. A systolic murmur of haemodynamic origin is often audible simultaneously with the diastolic murmur.

Acute aortic insufficiency must be differentiated from acute mitral insufficiency, which also sets in with an attack of dyspnoea and pain in the chest. Severe status asthmaticus and chest pain sometimes continue for several hours. A new murmur occupying entire systole appears at the same time as dyspnoea in acute mitral insufficiency. Acute aortic insufficiency is marked by two murmurs, systolic and diastolic. Acute mitral and acute aortic insufficiency at young age are usually complications of injury and bacterial endocarditis.

Acute aortic insufficiency sometimes develops as a *complication of bacterial endocarditis*. In some cases it develops as the result of ulceration of the aortic valve cusps, in others, as the result of their perforation which is often encountered in endocarditis induced by *Staphylococcus aureus* and gonococcus. Acute aortic insufficiency in endocarditis lenta is usually manifested by an attack of paroxysmal dyspnoea during which a new murmur is detected.

Aortic insufficiency sometimes develops in patients suffering from *atherosclerosis*, *syphilis*, *Marfan's syndrome*, *myxoedema* and certain other chronic diseases when they are apparently in good condition.

Its causes are as follows: deficiency of the aorta in myxoedema and Marfan's syndrome, rupture of the valve cusp ulcerated by an atheroma in atherosclerosis, and rupture of valve cusps which had undergone fibrosis in syphilis.

The clinical picture is rather monotonous in all cases. Sharp pain appears suddenly in the chest or epigastrium and is referred to the neck, arms, and back. Syncope often occurs during the pain and the patient suffers from fear of death. No signs of myocardial infarction are found. Physical examination reveals a loud diastolic murmur, simultaneously with which a systolic murmur is often heard. The peripheral signs of aortic insufficiency are very sharply manifested. The pulse arterial pressure is considerably increased. The diastolic pressure sometimes cannot be determined by auscultation.

Irrespective of its origin, acute aortic insufficiency follows a very unfavourable course. Immediately after its formation, attacks of paroxysmal dyspnoea appear and are soon joined by signs of right-ventricular failure. The disease usually terminates in death from collapse or heart failure.

The formation of a *dissecting aneurysm of the aorta* is attended by stretching of the aortic valve ring in approximately 10 per cent of cases. Aortic insufficiency is one of the consequences of this. Dissecting aneurysm of the aorta usually develops in elderly and old individuals with long-term high arterial hypertension and atherosclerosis of the aorta. The most common causes of its origin at a young age are congenital lesions of the aorta and its deficiency resulting from necrosis of its medial coat and giant cell aortitis in Marfan's syndrome and coarctation. In dissecting aneurysm of the aorta, the signs of aortic insufficiency appear at the same time as intolerable chest pain. A loud systolic murmur is often attendant to aortic insufficiency. The sharp appearance of aortic insufficiency, which seems to have no cause, in a patient with long-existing arterial hypertension provides grounds for suspecting dissecting aneurysm of the aorta. The suspicion is substantiated if other signs of dissecting aneurysm are revealed at the same time as aortic insufficiency. These signs are described in detail in the chapter 'Chest Pain'.

Aortic insufficiency sometimes develops in *aneurysm of Valsalva's sinus* which may be congenital or acquired. A small diverticulum at first forms in the wall of the sinus and then grows gradually in volume, separates the surrounding tissue of the heart and ruptures into one of its cavities. About 95 per cent of congenital aneurysms of this sinus arise from the walls of the non-coronary and right coronary sinuses and rupture into the right atrium or the right ventricle. Aneurysms of the right coronary sinus mostly rup-

ture into the right ventricle and only rarely into the right atrium. Aneurysms of the non-coronary sinus rupture into the right atrium, as a rule.

In some cases, aneurysm of Valsalva's sinus penetrates the cardiac septum, compresses one of the branches of His' bundle, thus causing disorders of conduction and even complete atrioventricular block. Compression of the coronary artery gives rise to pain in the region of the heart or the upper abdomen. Growth of the aneurysm may lead to disturbance in the function of one of the aortic valve cusps with the development of aortic failure. Rupture of Valsalva's sinus aneurysm into the heart cavity results in the formation of a shunt between the aorta and the pulmonary artery or between the aorta and the heart atria or ventricles. A shunt between the aorta and a heart cavity leads to abnormal loading of the right or left heart by blood entering it from the aorta. The formation of a shunt between the aorta and the pulmonary artery is attended by signs of aortopulmonary window.

Aneurysm of Valsalva's sinus is found more frequently in males. It ruptures soon after puberty, usually before the age of 30. Its rupture at an older age occurs very rarely. Patients survive the moment of the rupture, as a rule, if it is not attended by tamponade of the heart. Occasionally rupture of the aneurysm into the heart cavity is compatible with long survival. Patients who lived 15, 17 and 30 years after a rupture have been described. Death occurs from progressive chronic heart failure or, as we observed it in our practice, from concomitant bacterial endocarditis.

Heart failure in rupture of aneurysm of Valsalva's sinus always occurs acutely and is marked by regular replacement of the left-ventricular failure syndrome by the total heart failure syndrome. There is a period of apparent well-being between these two syndromes. The duration of this period is determined by the diameter of the shunt. Rupture of the aneurysm often occurs without any obvious cause or after physical exertion. Shortness of breath and pain in the region of the heart or upper abdomen appear immediately after the rupture. The pain syndrome predominates in the clinical picture of the acute period in most cases. In some instances, rupture of the aneurysm is mainly manifested by acute left-ventricular failure, whereas the pain sensations recede to the background.

The period of acute left-ventricular failure lasts from a few hours to a few days. A continuous murmur appears simultaneously over the heart region. The greater the volume of blood shunted from the aorta into the blood cavity, the more manifest are the pulsations of the carotids, an abrupt and bounding pulse in the radial artery, the increase in systolic arterial pressure, Duroziez's murmur, and other signs caused by rapid flow of blood from the arteries of the systemic circulation.

Aneurysm of Valsalva's sinus ruptures into the right atrium in most cases. As a consequence of this rupture the pulmonary circulation and the right and left heart are sharply overloaded with blood. The larger the diameter of the shunt, the sharper pulmonary hypervolaemia is manifested and the longer is the period of status asthmaticus. Clinical experience shows that the period of compensation following dyspnoea may last up to 30 years in some cases. In most instances, however, the continuous overload of the heart leads to the appearance of signs of chronic heart failure in the patient already by the end of the first year, the irrepressible advance of which causes death.

The difficulty of establishing the diagnosis of rupture of aneurysm of Valsalva's sinus is mainly due to the rarity of the disease. The combination of shortness of breath or paroxysmal dyspnoea with a more or less marked pain syndrome at the onset of the disease suggests myocardial infarction first of all. Similar clinical pictures arise sometimes in dissecting aneurysm of the aorta and acute mitral and acute aortic insufficiency. Acute left-ventricular failure in rupture of aneurysm of Valsalva's sinus, as in myocardial infarction, is attended by shortness of breath which is replaced by periods of paroxysmal dyspnoea. The pain syndrome may be absent in both diseases. When it is manifest, its appearance is attributed to compression of the coronary artery by the aneurysm. A case was described in which an aneurysm growing from Valsalva's sinus compressed the coronary artery and caused myocardial infarction. It is clear that the electrocardiographic signs of myocardial infarction make the diagnosis of rupture of aneurysm of Valsalva's sinus hardly probable, but do not rule it out completely.

The state of circulation after rupture of aneurysm of Valsalva's sinus and that in patent ductus arteriosus share many signs in common. Cases have been described when patients with rupture of this aneurysm were sent to be operated on for patent ductus arteriosus. Both diseases are marked by a continuous murmur and pulmonary circulation hypervolaemia. Heart failure takes an unfavourable course in both diseases and becomes irreversible within a relatively short time.

Each of these two diseases has many signs characteristic of it alone. Although both begin in childhood, heart failure develops gradually in patent ductus arteriosus, but acutely and often simultaneously with the pain syndrome in rupture of aneurysm of Valsalva's sinus. A continuous murmur is auscultated from childhood in a patient with patent ductus arteriosus, whereas in a patient with aneurysm of Valsalva's sinus it appears only after a shunt forms between the aneurysm and the heart cavities, i.e. after an acute disease in which acute left-ventricular failure had been the principal syndrome.

A short observation period and insufficient clarity of some of the signs may make the differential diagnosis between patent ductus arteriosus and rupture of aneurysm of Valsalva's sinus difficult. In such cases special methods of examination are applied, the patient's condition permitting. Aortography is the most important among them. The contrast medium is injected into the region of the aortic orifice. In rupture of aneurysm of Valsalva's sinus, the contrast medium enters one of the heart cavities early and the pulmonary vessels some time later. Early contrasting of the pulmonary artery is a characteristic sign of patent ductus arteriosus. Of no less diagnostic significance is the detection of the shadows of a contrasted ductus arteriosus and of aneurysm of Valsalva's sinus at the origin of the aorta.

Acute aortic insufficiency follows a very unfavourable course irrespective of its origin. Immediately after the disease develops attacks of paroxysmal dyspnoea appear, soon joined by signs of right-ventricular failure. The disease usually terminates in death from collapse or heart failure. Aortography is advisable in all cases when one of the rare causes of aortic insufficiency or the association of aortic insufficiency with other congenital heart diseases is suspected. When there is no doubt that the patient is suffering from aortic insufficiency, aortography makes it possible to appraise its severity.

Supplement XIV-1

Causes and Types of Heart Failure

1. Right-ventricular failure.
   - Pulmonary insufficiency.
   - Pulmonary stenosis.
   - Tricuspid insufficiency (Ebstein's anomaly).
   - Tricuspid stenosis.
   - Tumours of the heart (subacute cor pulmonale).
   - Carcinoid tumour.
   - Myxoma of the right atrium.
   - Chronic cor pulmonale.
2. Biventricular heart failure.
   - Myocarditis.
   - Congestive cardiomyopathy.
   - Fibroplastic parietal endocarditis.
   - Endocardial fibroelastosis.
   - Amyloidosis of the heart.
3. Left-ventricular failure.
   - Mitral stenosis.
   - Atrial septal defect.
   - Myxoma of the left atrium.
   - Mitral insufficiency.
     - Chronic.

Congenital.
Acute.
Aortic stenosis.
Subaortic (hypertrophic) stenosis.
Aortic insufficiency.
Chronic.
Acute.
Dissecting aneurysm of the aorta.
Aneurysm of Valsalva's sinus.

Supplement XIV-2

Causes of Chronic Cor Pulmonale

1. Diseases of pulmonary parenchyma.
   Chronic bronchitis with or without emphysema and asthma.
   Chronic pneumonia with pulmonary fibrosis and bronchiectasis.
   Diffuse interstitial pulmonary fibrosis with or without emphysema (fibrocaseous tuberculosis, pneumoconiosis, sarcoidosis, Hamman-Rich syndrome, diffuse reticular pneumosclerosis).
2. Diseases of the pulmonary vessels.
   Primary pulmonary hypertension.
   Recurrent embolism of the pulmonary vessels.
   Periarteritis nodosa.
   Amyloidosis.
   Miliary carcinomatosis of the lungs.
   Haemoglobinopathies.
   Parasitic pulmonary diseases.
3. Diseases of the thorax with restriction of its mobility and with hypoventilation.
   Kyphoscoliosis ('heart failure in humpbacks').
   Obesity (Pickwick's syndrome).
   Thoracoplasty.

Chapter XV

Heart Murmurs

Heart murmurs are perceived and appraised much easier than the heart sounds. Another reason for accepting murmurs as a differential diagnostic criterion is that their relation to the phases of the cardiac cycle may be determined on the basis of auscultation alone. Phonocardiography does not replace the auscultation of murmurs. It may only demonstrate more precisely their relationship with the heart sounds in time.

Systolic, diastolic and continuous murmurs are distinguished according to their duration and time of occurrence. Soft (grade 1 or 2 according to a six gradation scale), clear or moderately loud (grade 3), loud without a thrill (grade 4), and loud attended by a thrill (grades 5 and 6) murmurs are distinguished according to intensity. Diastolic and continuous murmurs are evidence in most cases of organic diseases of the cardiovascular system, whereas systolic murmurs are often encountered in individuals with no signs of heart or vascular diseases. A murmur is called *organic* if it occurs as a consequence of any disorders in the normal anatomical structure of the heart septum or valve structures. An *innocent* murmur is one that is heard in persons with no objective signs of disturbance in the normal morphological structure of the heart and vessels. The term 'functional murmur' is hardly a fortunate designation. In manuals of propedeutics (preliminary instruction in the field of internal diseases) the term 'functional' designates a systolic murmur heard over the heart apex in anaemia, for instance, although the heart in this case may be enlarged and the fibrous ring of the mitral valve distended. A systolic murmur appearing over the pulmonary artery at the beginning of pregnancy and disappearing soon after delivery, or a systolic murmur over the abdominal aorta in healthy children is an axample of an innocent murmur. A systolic murmur heard in the initial period of rheumatic carditis or a systolic murmur in a person with a bicuspid aortic valve cannot be called innocent because their underlying factors are organic processes which, advancing with time, may lead to the development of a heart valvular disease. A murmur heard during the very first examination of a patient cannot, of course, be regarded 'innocent', but a tentative designation of the murmur by this term placates the patient and his relatives, giving the physician grounds for repeating the examination till he becomes convinced of its innocent character or

its association with some organic heart disease. Facts accumulated to date leave no doubt that the conception of the association of the shape of the murmur with the direction of the blood stream through the valve is false. A diamond shape of the murmur in the second right intercostal space may be encountered both when the blood stream flows in a normal direction through the aortic valve and when it is regurgitated through the interventricular septum or through the mitral valve. In accordance with the abovestated, we constructed a scheme for the differential diagnosis of heart murmurs based on the principle of their maximum audibility at definite points of the body surface.

Innocent Murmurs

Murmurs audible in a healthy person are innocent (Supplement XV-1). The cause of their origin is still not clear. They are usually heard best in the second to fifth intercostal spaces at the sternal edge. Extracardiac and intracardiac innocent murmurs are distinguished. The **cardiopulmonary extracardiac murmur** had already been described by Laennec who claimed that the decrease in the dimensions of the heart during systole causes decompression of the adjacent areas of the lungs. Their filling with blood produces a high-frequency murmur. Occurring during each systole, it is appraised by us as a systolic murmur. A diastolic cardiopulmonary murmur produced by compression of pulmonary tissue adjacent to the heart is an exceptionally rare occurrence. Inflammatory processes in the pericardium and anterior mediastinum sometimes lead to fusion of the pericardium with the pleura and with chondrosternal or chondrocostal articulations. Contraction of the heart in such cases causes vibration of the adhesions themselves and of the involved articulations. The murmurs which arise in this case often have a musical character.

Innocent murmurs are usually intracardiac in origin. According to the findings of intracardiac phonocardiography, a systolic murmur is always recorded in the pulmonary artery of a healthy person. It cannot be auscultated with a stathoscope. Under the effect of the accelerated blood flow, these subthreshold vibrations of the structures of a normal pulmonary artery valve are noticeably intensified and perceived as a systolic murmur. The stated viewpoint finds indirect verification in clinical practice. To be sure, innocent murmurs are encountered particularly often in anaemia, thyrotoxicosis, pregnancy and other conditions characterized by increased minute volume. This does not mean, however, that all murmurs heard in the hyperkinetic syndrome are innocent. A murmur can be related to the group of innocent murmurs only if thourogh examination and

long-term follow-up provide no grounds for making the diagnosis of some heart disease.

Innocent murmurs may be **systolic** or **continuous**. Their intensity ranges from soft to moderately loud. The harsher the murmur, the more probable its organic origin. There is an exception to this rule. The murmur of parasternal vibration is often harsh, although it is an innocent murmur. Innocent murmurs are always short. They are never pansystolic. They occupy only the middle or the end of systole. Unfortunately many organic murmurs are short and also occupy only the beginning or the end of systole. Innocent murmurs usually radiate well along the entire precordial region, whereas organic murmurs are sometimes heard only at some one point. Innocent murmurs are usually intensified during inspiration. Only a cardiorespiratory murmur disappears when the breath is held. The intensity of innocent murmurs, just as the intensity of organic murmurs, increases noticeably under the effect of physical exercise. All innocent murmurs are best heard when the patient is in a supine position. Innocent murmurs may be divided into systolic and continuous murmurs (Supplement XV-1).

Vibration (parasternal) murmur is often heard in children and adolescents and much less frequently in young men and girls. It begins from the first sound and occupies one half or two thirds of systole. It is usually detected at the left sternal edge. The murmur is always musical. Still described this murmur as the vibration or the sound produced by a string. The third or fourth intercostal space is usually the site of its maximum loudness, but sometimes it may be heard in the second left intercostal space and at the heart apex as well. Physical exercise and fever intensify the murmur. It is believed that Still's murmur occurs under the effect of vibration of the cusps of a normal pulmonary valve. Organic systolic murmurs of the same localization are distinguished from it by the degree of the attendant symptoms and signs of the diseases of the cardiovascular system.

Supraclavicular (carotid) murmur is best heard above the clavicle. It is almost always louder above the right than above the left clavicle. It is also clearly heard in the retrosternal fossa. It is spindle-shaped on the phonocardiogram and occupies only the first half of systole. The murmur is often loud and may be referred to the base of the heart where it is sometimes mistaken for the murmur of aortic or pulmonary stenosis. The supraclavicular murmur is encountered very often. In mass-scale examination it is detected in 30 to 40 per cent of students. It is found still more frequently among children. Compression of the subclavian artery results in disappearance of the murmur.

The supraclavicular murmur of atherosclerotic origin is best heard at the outer edge of the sternocleidomastoid muscle. It is

distinguished from an innocent murmur by a lower pitch and longer duration. It may occupy entire systole, but is more often related to continuous murmurs, i.e. it occupies systole and part of diastole. The carotid arteries in these patients are usually dilated and tortuous. Their intensified pulsation is easily revealed by inspection and palpation. The supraclavicular murmur which we encountered in patients with arteritis of the aorta and its branches was always continuous. It ranged in intensity from soft to loud. It was always loudest at sites of aorta auscultation, namely, in the second right intercostal space and in the retrosternal fossa. When the subclavian artery is compressed, the murmur does not disappear and does not even diminish in intensity. High differential diagnostic significance should be attached to the patient's age and general condition, to the character of the concomitant symptoms and signs of the disease. The murmurs of aortic and pulmonary stenosis occupy entire systole and not only part of it. They are much louder than the innocent subclavian murmur, as a rule. Their intensity is maximum in the second right and left intercostal spaces and not above the clavicle.

The **pulmonary systolic murmur** is detected both in children and in adults. Its maximum intensity is in the second left intercostal space at the sternal edge. It is sometimes referred upward to the base of the neck and to the left. The murmur is usually spindle-shaped and occupies the first half of systole. The pulmonary murmur is always of a blowing and not of a musical character. It may be soft or moderately loud. In rare cases it is loud, but is never attended by a thrill. The murmur is best heard when the patient is lying down. The pulmonary murmur is intensified under the effect of physical exercise, agitation and fever. Expiration improves the audibility of this murmur. The pulmonary murmur is heard particularly often in frail children. It is always heard in adults with mildly pronounced kyphosis of the thoracic spine. Proper caution should be exercised in the clinical evaluation of the pulmonary systolic murmur. Many congenital and acquired heart diseases are attended by a systolic murmur which does not differ from the innocent pulmonary murmur in localization and properties. Attention focused on the concomitant symptoms and signs enables the physician to avoid a diagnostic error.

An innocent **aortic systolic murmur** is encountered less frequently than the pulmonary murmur. It is believed that it results from systolic vibration of the distended aortic root. Its musical character is often explained by the periodic regularity of vibrations of the valve cusps at the site of their attachment. The murmur occupies the middle of systole. Its intensity ranges from soft to moderately loud. Its maximum intensity is in the second intercostal space at the sternal edge. The murmur is usually transmitted to the heart apex. This murmur may be considered innocent only in young in-

dividuals with normal arterial pressure. In elderly patients with elevated arterial pressure the aortic systolic murmur should be regarded sclerotic. It differs from the innocent aortic systolic murmur only by the presence of the concomitant malady.

Abdominal murmur. An innocent systolic murmur over the abdominal aorta is detected quite frequently in children and adolescents. It is soft, short and heard only at the beginning of systole. It is best audible on the midline of the abdomen between the xiphoid process and the navel. It is not transferred to the sides of the midline. In stenoses of the coeliac, renal and mesenteric arteries the abdominal murmurs may be systolic or continuous. Their loudness is determined by the degree of the arterial stenosis. As it is noted above, an innocent abdominal murmur is always soft, systolic and not transmitted to any point.

The group of innocent murmurs includes the **venous hum (murmur)** and the **mammary murmur.** Both of them are continuous. The former is regularly heard over the external jugular vein in severe anaemia. It was previously called the 'venous hum' or the 'hum murmur'. The mammary murmur is detected over the mammary glands at the end of pregnancy and during lactation.

Continuous Murmurs

A murmur is called continuous if it begins during systole, continues after the second heart sound and usually occupies part of diastole. Sometimes it may be audible during part of systole and entire diastole. In all cases, the continuous murmur encompasses the second heart sound from both sides. Its systolic and diastolic components arise under the effect of one and the same cause. At the site where the continuous murmur arises, the blood flow does not change direction within the entire period of its audibility. In this the continuous murmur differs from the systolic and diastolic murmurs following one another whose origin (e.g. in mitral stenosis and mitral insufficiency) is linked with changes in the direction of the blood flow although they form at the same site. Continuous murmurs arise (Supplement XV-2) as a consequence of blood shunting in arterial stenosis or dilatation and in increase of the flow of blood through a vessel.

Blood shunt. *Patent ductus arteriosus* is evidently the most common cause of a continuous murmur. Sometimes this murmur detected on physical examination of a child or adult proves to be the only sign of the malformation. The murmur begins some time after the first heart sound and not immediately after it. It grows in intensity with the increase of pressure in the aorta. The pressure gradient between the aorta and pulmonary artery reaches maximum at the end of systole. Maximum intensity of the murmur is noted at the

same time. With the beginning of diastole, the pressure in the aorta starts diminishing, which is attended by a corresponding decrease in the intensity of the murmur. Maximum intensity of the murmur coincides in time with the second sound. The murmur ends in the middle or the second half of diastole. It is often accompanied by a thrill. Maximum intensity of the murmur and thrill are in the second intercostal space, from where they are transmitted to the third intercostal space. When the murmur is very loud it is audible over the entire heart area. The murmur of patent ductus arteriosus is heard with equal intensity both on inspiration and on expiration. It intensifies when the patient is in a supine position. The systolic component of the murmur is always of a longer duration and louder than the diastolic component.

In patent ductus arteriosus the pulmonary circulation and the left heart are overfilled with blood. The greater the excessive load, the more pronounced are the signs of pulmonary hypervolaemia and the more frequently is the third heart sound encountered. With the development of pulmonary hypertension, the diastolic component of the continuous murmur gradually becomes shorter till it eventually disappears. Instead of it a third heart sound is heard during diastole, which is attended by a short mesodiastolic murmur. With the development of pulmonary hypertension, the systolic component of the continuous murmur becomes shorter and may completely disappear. Only the ejection sound is heard instead of it at times. When blood pressure in the pulmonary artery exceeds that in the aorta, the direction of the blood flow through the shunt alters. This is manifested clinically by cyanosis. The flow of blood through the shunt in the pulmonary artery-aorta direction is not attended by a murmur. Long-term pulmonary hypertension leads to intensification of the second sound over the pulmonary artery and to distension of the fibrous ring of the pulmonary heart valve. The characteristic diastolic murmur of pulmonary insufficiency appears. Signs of right-ventricular failure usually appear simultaneously with the diastolic murmur. The differential diagnosis of these signs is discussed in another section.

The *cervical venous hum* is sometimes best audible not over the sternocleidomastoid muscle where this muscle is attached to the medial end of the clavicle, but at the sternal edge in the first or second intercostal space where it is sometimes mistaken for the continuous murmur of patent ductus arteriosus. A venous hum of unusual localization is distinguished from the murmur of persistent ductus arteriosus by the fact that its diastolic component is louder than or of the same intensity as the systolic component. The diastolic component of the patent ductus arteriosus murmur is always softer and shorter than the systolic component. The cervical venous hum is usually clearly audible when the patient is standing and

diminishes and disappears completely when he is lying down. The murmur of patent ductus arteriosus is best heard when the patient is in a supine position and diminishes in intensity when he changes to a vertical position. When the jugular vein is compressed above the clavicle, the cervical venous hum disappears completely or sharply diminishes in intensity. This manipulation does not affect the intensity of the murmur in persistent ductus arteriosus.

The *mammary murmur* is best heard in the second intercostal space close to the sternum. Sometimes it is of maximum intensity in the third or even fourth intercostal space. When it is heard on the left side of the chest, this murmur may be mistaken for the murmur of persistent ductus arteriosus. Compression with the finger on the lateral side of the stethoscope or compression with the stethoscope itself leads to the disappearance of the mammary murmur but has no effect on the intensity of the murmur of persistent ductus arteriosus.

Aneurysm of Valsalva's sinus may be congenital or acquired. After the aneurysm ruptures a shunt forms the localization and size of which determine the auscultation picture of the disease. The main signs of tearing of the aneurysm are shortness of breath and the pain syndrome simultaneously with which a continuous murmur appears. The acute period of the disease is replaced by an asymptomatic period during which the patient makes no complaints but physical examination reveals a continuous murmur which remains throughout life. It is loudest at the left edge of the sternum at its midlevel in rupture of the aneurysm into the right ventricle. Its maximum loudness at the level of the lower third of the sternum to the right or left of it is usually evidence of rupture of the aneurysm into the right atrium. The murmur is often attended by a thrill. Most authors claim that in rupture of Valsalva's sinus the diastolic component of the murmur is louder than the systolic component. In the case, which occurred in our practice, this murmur was soft and the systolic component was louder than the diastolic.

Maximum intensity of the murmur in persistent ductus arteriosus is around the second sound. In rupture of Valsalva's sinus the murmur is loudest either in systole or in diastole; minimum and not maximum of the murmur is always localized around the second heart sound.

The character of arterial pressure changes in rupture of Valsalva's sinus depends on the diameter of the shunt formed. The greater the diameter of the shunt, the more marked is the complex of peripheral signs developing under the effect of the rapid flow of blood from the aorta (a quick and bounding pulse, Duroziez' murmur, reduced diastolic pressure, capillary pulse, carotid shudder, and a systolic sound over the brachial artery). These signs are manifested much more sharply in rupture of aneurysm of Valsalva's sinus than in

persistent ductus arteriosus. The final diagnosis is established from the results of aortography.

The auscultative signs of *coronary arteriovenous aneurysm* are not uniform. They change sharply depending on the localization of the communication. A continuous murmur is only heard in coronary aneurysms communicating with veins localized on the surface of the atrium. The coronary blood flow is always greater during diastole than during systole, and the diastolic component is therefore louder than the systolic component. The localization and pitch of the murmur fully coincide with those of the continuous murmur in aneurysm of Valsalva's sinus. Coronography reveals a coronary arteriovenous aneurysm and shows its localization.

A continuous murmur is a constant auscultative sign of *pulmonary arteriovenous aneurysm.* As in other arteriovenous aneurysms found at a remote distance from the heart, the systolic component of this continuous murmur in a patient with such an aneurysm is louder than the diastolic. The murmur is well heard over the entire surface of the lungs and not only in the precordial region. Pulmonary arteriovenous aneurysm differs from persistent ductus arteriosus by the localization of the murmur and the presence of characteristic shadows in the lungs. Pulmonary arteriography is resorted to in doubtful cases.

A continuous murmur in *arteriovenous aneurysms in systemic circulation* is usually attended by a thrill which noticeably simplifies the search for and the diagnosis of the disease. The 'tinkling of a sunken bell' is often produced when the region of the aneurysm is compressed with a hard stethoscope. Most of these aneurysms are of traumatic origin. If the diagnosis is nevertheless doubtful, arteriography is performed and it demonstrates the presence of an arteriovenous communication.

Arterial stenosis or dilatation. Stenosis of any artery is always combined with a systolic murmur arising under the effect of accelerated blood flow through the constricted segment. The murmur becomes continuous when the pressure gradient at the ends of the stenosed segment also persists during even a part of diastole. During the entire cardiac cycle, blood pressure before the constricted area of the aorta in its *coarctation* is much higher than the pressure in the post-stenotic segment. Moreover, the post-stenotic segment of the aorta is always dilated and an aneurysm with a characteristic turbulent blood flow forms sometimes. A powerful network of arterial collaterals develops between the aortic segments located distal and proximal to the site of its constriction. Small aneurysms sometimes also form at the site where the collateral arteries drain into the aorta. The increased flow of blood through these and other collateral arteries contributes to the origin of continuous murmurs whose maximum intensity is heard during systole.

A continuous murmur is sometimes audible in *congenital stenosis and parietal thrombosis of branches of the pulmonary artery.* It is usually heard not only in the precordial region, but also over pulmonary areas some of which are remote from the heart. The systolic murmur is mostly encountered in *aneurysm of the aorta* and *in arteritis of the aorta and its branches.* Continuous murmurs are occasionally encountered in these diseases. Their origin is linked with a turbulent blood flow in the aorta and in arterial segments localized distal to their constriction.

Increase in the volumetric rate of blood flow through a vessel. An increased blood flow through a vessel may be the cause of both a systolic and a continuous murmur. The venous hum is the most commonly known example of this. According to the localization, cervical and abdominal venous hums are distinguished. The *cervical (venous) hum* is an innocent murmur. It is heard and recorded on the phonocardiogram continuously both during systole and during diastole. This distinguishes it from the murmurs in aortic and pulmonary stenoses which, in combination with insufficiency of the aortic or pulmonary valves, consist of systolic and diastolic murmurs separated by an interval during which no murmur is audible. In patent ductus arteriosus the systolic component of the murmur is louder while the systolic component of the cervical venous hum is softer than the diastolic component. The cervical venous hum is best heard over the medial end of the clavicle and is intensified when the patient's head is turned to the side contralateral to that on which it is audible. It disappears when the external jugular vein is compressed. The continuous venous hum sharply diminishes and often even disappears when the patient changes from a vertical to a horizontal position.

The *abdominal venous hum* is heard in the region of the navel or xiphoid process. It is a continuous murmur and its systolic component is louder than the diastolic. Sometimes for reasons as yet unknown, it diminishes in intensity and may even disappear completely for some time. The hum sometimes radiates to very considerable distances and may be audible in the region of the heart or on the back. A continuous venous hum is also heard in the epigastrium when the portal vein is compressed by a tumour or an enlarged lymph node. A vascular tumour of the liver is occasionally its source.

Systolic Murmur

The number of clinical syndromes which must be recognized becomes much less if a differential diagnosis is made separately of a systolic murmur with maximum intensity at the heart apex, one heard at the site of auscultation of the aorta and one heard at the site of auscultation of the pulmonary artery.

A **systolic murmur over the heart apex** is usually caused by *mitral insufficiency* resulting from incomplete separation of the left heart cavities during systole. The differential diagnosis of mitral insufficiency from diseases and syndromes listed in Supplement XV-3 begins with analysis of the heart sounds. In a healthy person, splitting of the second sound during inspiration occurs because its pulmonary component is delayed. If only the second sound is heard during expiration and is split at the peak of inspiration, the diagnosis of pulmonary arterial stenosis and atrial and ventricular septal defect may be ruled out almost with assurance. In an atrial septal defect both heart ventricles receive blood from the communicating atria and the wide splitting of the second sound in this disease is therefore fixed. In severe mitral insufficiency a third heard sound is always audible. It may be accompanied by a short (mesodiastolic) murmur which is sometimes mistaken for the presystolic murmur of mitral stenosis.

The systolic murmur is practically always attendant to mitral insufficiency. It begins immediately after the first sound and continues up to the beginning of the second. Sometimes it continues after closure of the aortic valve and ends just before the pulmonary artery valve closes. The mitral insufficiency murmur may be of uniform intensity throughout systole, but it may also become much louder towards the end and thus resemble the systolic murmur heard in aortic stenosis and ventricular septal defect. This happens in rupture of the chordae tendineae. The sound of aortic valve closure is diminished because of the systolic murmur. A similar diminution of the aortic component of the second sound is found in aortic stenosis.

In cases of chronic mitral insufficiency, the continuous systolic murmur is of a blowing character, in cases of acute mitral insufficiency, it may be musical. The musical murmur of mitral insufficiency and the musical murmur of aortic insufficiency transmitted to the heart apex often cannot be distinguished from each other by auscultation. The shape of the pulse wave discloses the mechanism of the murmur in such cases. In some instances of mitral insufficiency, the murmur is audible only in the first half of systole. It is probably caused by the increased blood flow through the valve during rapid filling of the ventricle. It is indistinguishable auscultatively from the early systolic murmur in small ventricular septal defects. *Atherosclerotic cardiosclerosis* is often attended by mitral insufficiency the characteristic sign of which is a late systolic murmur. The murmur does not begin immediately after the first heart sound, but appears in the middle or even only at the end of systole. It may be presumed that the origin of the late systolic murmur is caused by malfunction of the left-ventricular papillary muscles.

In cases of *ventricular septal defect* the systolic murmur results

from blood shunt from the left into the right ventricle. It lasts throughout systole when there is no pulmonary hypertension. It differs from the systolic murmur of mitral insufficiency in localization rather than in quality. The zone of its maximum intensity is at the left sternal edge usually in the fourth or fifth intercostal space. In large ventricular septal defects the systolic murmur can be hardly audible.

Tricuspid insufficiency is also marked by a murmur which may last throughout systole. It is best heard on the left at the sternal base but in cases with a drastically increased right ventricle it is also well heard at the heart apex. It never intensifies at the end of systole. A study of the venous pulse allows systolic murmur of tricuspid insufficiency to be distinguished from a similar murmur of mitral insufficiency.

Mitral insufficiency is encountered in many congenital and acquired heart diseases differing from one another in the clinical course and therapeutic methods; it is therefore necessary to reveal its cause in each case. *Congenital isolated mitral insufficiency* is a very rare disease. In such cases the systolic murmur is heard from birth or from infancy and there is no history of rheumatic fever or bacterial endocarditis. Mitral insufficiency is often a component of other congenital heart diseases. In Marfan's syndrome it is either a consequence of extreme elongation of the chordae tendineae or the result of myxomatous degeneration of the valve cusps. It does not alter the clinical course of the syndrome. The course of other congenital heart diseases, in which mitral insufficiency is among the syndromes, does not alter either. Among these diseases are *endocardial fibroelastosis* and *endocardial myofibrosis*. Acquired mitral valvular insufficiency is caused by anatomical destruction of the valve cusps, subvalvular insufficiency by a lesion of the subvalvular structures (papillary muscles, chordae tendineae), and mixed insufficiency is caused by impaired function of the valve whose cusps and subvalvular structures are anatomically intact.

Rheumatic endocarditis is the most common cause of mitral valvular insufficiency. Pure mitral insufficiency is a rare consequence of rheumatoid valvulitis. It is usually combined with mitral stenosis. The differential diagnosis between them may be established by studying the changes in the apical systolic murmur. The systolic murmur of mitral insufficiency appears in the acute period of rheumatic fever. The persistence of this early systolic murmur after the acute period of the disease ends is a characteristic feature. In cases of rheumatic fever complicated by mitral stenosis, the end of the acute period of the disease is marked by complete disappearance of the murmur. The characteristic auscultative picture of mitral stenosis appears only after a more or less long period of time during which the heart sounds remain clear.

Endocarditis lenta takes second place in frequency as the cause of mitral insufficiency. The bacteria may form colonies on the intact valve but especially frequently thrombo-ulcerative endocarditis develops on valves which had already undergone changes. As a consequence of this, mild mitral insufficiency develops into the severe form. *Septic endocarditis* with localization of the process on the mitral valve leads to the appearance of a characteristic systolic murmur over the heart apex. In patients with already existing mitral insufficiency the existing murmur changes in character. Both the appearance of the systolic murmur and the change in its character testify to progressive valve destruction and should be considered as an indication for repeating blood cultures for isolating the bacteria.

Subvalvular mitral insufficiency originates in association with rupture or malfunction of the papillary muscles or in association with rupture of the chordae tendineae. A sudden appearance of a harsh systolic murmur in a formerly healthy person usually over 50 years of age is a typical sign of mitral insufficiency consequent upon rupture of the chordae tendineae. A harsh systolic murmur occurs in disturbed function of the posterior cusp. It cannot be distinguished by auscultation from the systolic murmur of aortic stenosis. Rupture of the chordae tendineae which hold the anterior mitral valve cusp in place leads to the appearance of a loud systolic murmur which is often transmitted clearly to the interscapular space. It is sometimes audible on the head. The sinus rhythm found in the patient before the illness usually persists after the heart disease develops. An atrial gallop rhythm is detected by auscultation and on the phonocardiogram in more than 50 per cent of patients with acute mitral insufficiency.

Acute mitral insufficiency sometimes occurs in *myocardial infarction* marked by involvement of the papillary muscles. The posterior papillary muscle is affected more frequently. If the patient survives the rupture, a harsh systolic murmur of acute mitral insufficiency is audible against the background of status asthmaticus. Affection of the papillary muscles in less extensive infarcts is attended by the development of a late systolic murmur which is diamond-shaped on the phonocardiogram. Its intensity and pitch may alter noticeably with each day. The murmur may disappear a few days after its origin. A late systolic murmur is also often auscultated and recorded in patients with sclerotic degeneration of the left-ventricular papillary muscles. The first heart sound preserves its high pitch, whereas in chronic mitral insufficiency it is diminished, as a rule.

Marked *dilatation of the left ventricle and the fibrous mitral valve ring* always result in mitral insufficiency. Some authors call it relative, others mixed. It is often encountered in anaemia, arterial

hypertension, aortic stenosis, cardiosclerosis, thyrotoxicosis and other diseases and syndromes. Mitral insufficiency in these diseases is manifested all the greater depending on the severity of the patient's condition. As the patient's general condition deteriorates the auscultative signs of relative mitral insufficiency become more pronounced. Improvement of the patient's general condition under the effect of treatment is usually attended by the disappearance of the mesodiastolic murmur while the diastolic murmur of mitral valvular stenosis becomes clearer. With the growth of heart failure, the auscultative picture of mitral stenosis becomes less manifest: the loud character of the first sound decreases and the heart murmurs become less intensive.

Marked *calcification of the valve fibrous ring* is manifested by the picture of mitral insufficiency, either mild or severe. The diagnosis may be made after detecting signs of calcification on heart radiographs of elderly and aged females with no history of rheumatic fever. Calcification of the mitral valve is demonstrated on the echocardiogram as an intensive band moving in parallel to the movements of the left-ventricular posterior wall. In some cases the calcification shadow is superimposed on the shadow of the posterior mitral valve cusp.

Mitral insufficiency is found in 40 to 100 per cent of cases of *muscular-type subaortic stenosis*. Angiocardiography shows that in such cases blood is usually regurgitated at the end of systole. The regurgitation occurs because the anterior valve cusp is drawn into the left-ventricular cavity by the hypertrophied medial papillary muscle. The final diagnosis is established from the results of ventriculography or echocardiography. Hypertrophy of the interventricular septum on the echocardiogram and the characteristic dumbbell shape of the left ventricle on the ventriculogram are typical signs of the disease. *Deficiency of mitral valve prosthetics* develops either immediately after the operation or at different periods after it. It results either from disorders in the function of the prosthesis or from distension of the fibrous valvular ring. Mitral insufficiency in *left-ventricular aneurysm* may be a consequence of involvement of the left-ventricular papillary muscles in the infarction or simple systolic distension of the ventricles with displacement of the intact papillary muscles. Marked left-ventricular dilatation is the third cause of the development of mitral insufficiency.

Tricuspid insufficiency develops as a result of incomplete separation of the right heart cavities during systole. Congenital tricuspid insufficiency is very rare. Most cases of *tricuspid valvular insufficiency* are of rheumatic origin. Lupus endomyocarditis and carcinoid tumour are sometimes its causes. Postoperative tricuspid insufficiency develops after commissurotomy performed for tricuspid stenosis. Rare cases of traumatic tricuspid insufficiency devel-

oping after a heart injury may also be included in this group. The incidence of tricuspid insufficiency of bacterial origin has noticeably grown in recent years. It is usually one of the manifestations of sepsis. In *Ebstein's disease*, congenital tricuspid insufficiency is commonly encountered in conjunction with atrial septal defect. There is no cyanosis in mild cases of this disease and it is sometimes mistaken for tricuspid insufficiency.

Subvalvular tricuspid insufficiency may be caused by congenital or acquired malfunction of the papillary muscles. Endocardial fibroelastosis is an example of the former, and ischaemia or necrosis of the papillary muscles is an example of the latter. The spatial relationship between the valve cusps and the papillary muscles holding them is regularly disturbed in distension of the right-ventricular cavity. Pulmonary hypertension is the most common cause of this disorder. A similar mechanism of the development of relative tricuspid insufficiency is encountered in pulmonary stenosis.

Tricuspid insufficiency in cardiomyopathy, anaemia and thyrotoxicosis is of complex origin. It is a consequence both of right-ventricular dilatation and of dystrophic changes in the papillary muscles. Myxomatous degeneration of one of the valve cusps results in its retraction into the right-ventricular cavity during systole and in the development of tricuspid insufficiency, the diagnosis of which is based on the characteristic syndrome of a midsystolic sound with postsystolic murmur. Relative tricuspid insufficiency is always attendant to severe right-ventricular failure of any origin. It is found especially often in decompensation of left heart diseases, in cardiomyopathy, and in pulmonary hypertension. Valvular tricuspid insufficiency is rare.

Marked right-ventricular hypertrophy leads to axial deviation of the heart. The left ventricle in such a case is shifted to the back and a greater part than usual of the anterior heart surface is formed by the right ventricle, which sometimes even forms the heart apex. As a result of this deviation the systolic murmur of tricuspid insufficiency is best audible in the third and fourth left intracostal spaces at the sternum and is transmitted to the heart apex. In cases of less marked right-ventricular hypertrophy, the systolic murmur is best heard at the attachment of the xiphoid process to the sternum and in the third or fourth right intercostal spaces at the sternum. It is never transmitted to the left axilla.

Tricuspid insufficiency is rarely found as an isolated lesion. In most cases it is attendant to some other disease or is its complication. The symptoms and signs of the principal disease usually predominate in the clinical picture. The attendant tricuspid insufficiency is nevertheless capable of changing the course of the main disease and introducing some additional signs. In practice, the systolic murmur of tricuspid insufficiency often has to be differentiated

from the similar murmur of mitral insufficiency. They differ from each other in irradiation and changes in intensity depending on the respiratory phases. The systolic murmur of tricuspid insufficiency is often intensified at the peak of inspiration, whereas the murmur of mitral insufficiency becomes louder during expiration. The degree of this sign is determined by the heart contractile function. The severer the heart failure, the less the systolic murmur intensifies during inspiration.

The systolic murmur of tricuspid insufficiency is not transmitted to the left axilla even when the heart apex is formed by the right ventricle. In doubtful cases, a precordial systolic murmur should be considered tricuspid if it is audible between the xiphoid process and the heart apex but is not heard between the apex and the left axilla. Moreover, the systolic murmur of tricuspid insufficiency is distinguished by instability. It often changes in intensity in one and the same patient and may disappear completely in severe heart failure. The murmur arising on the mitral valve is distinguished by firm stability.

It is often necessary to distinguish valvular tricuspid insufficiency from relative insufficiency. They differ from each other in the degree and reversibility of this or that sign and not in its presence or absence. Intensive therapy of heart failure is the best method for their differentiation.

A systolic murmur in the second right intercostal space is most commonly a manifestation of **aortic stenosis** whose characteristic sign is obstruction of the flow of blood from the left ventricle. Valvular, supravalvular and subvalvular stenosis are distinguished according to the localization of obstruction, and congenital and acquired according to the origin. The most common type is valvular aortic stenosis. In more than half cases it is encountered at the same time as mitral stenosis. Its rheumatic aetiology in such cases gives no room for doubt. Isolated aortic stenosis may be congenital or acquired.

Congenital aortic stenosis may be valvular, supravalvular or subvalvular. Stenosis consequent upon developmental anomaly of the aortic valve is encountered most commonly. Aortic stenosis with unicuspid, bicuspid or tricuspid valves is distinguished. When the characteristic systolic murmur appears not at birth but at a later period, the condition is called *acquired aortic stenosis*. Two types of acquired valvular aortic stenosis may be distinguished, namely, rheumatic and sclerotic. In all cases stenosis of the aortic orifice results from restricted mobility of the valve cusps due to the development of coarse fibrous tissue in them or due to calcium salt deposits. Isolated aortic stenosis in elderly and old individuals develops because of fibrosis of the valve cusps which do not adhere together although they lose their mobility. Congenital unicuspid

and anomalous tricuspid valves always narrow the aortic orifice and in a child with these anomalies a systolic murmur is audible from birth. At birth the cusps of the bicuspid valve are often very mobile and do not constrict the aortic orifice. As the years go by, they calcify and lose their mobility. This leads to the appearance of a systolic murmur and the development of aortic stenosis.

The systolic murmur is the most common sign of aortic stenosis. On the phonocardiogram it is usually spindle-shaped, beginning a few hundredths of a second after the first heart sound and ending before the aortic component of the second sound begins. The ejection sound preceding the systolic murmur is detected in many cases. With the gradual calcification of the valve, the ejection sound and the aortic component of the second sound diminish and may disappear completely. In observing the same patients in the periods of compensation and decompensation it is easily seen that the duration and intensity of the murmur are determined by the functional state of the left ventricle rather than by the severity of aortic stenosis. The severer the decompensation of the disease, the softer is the systolic murmur. In our experience we failed to hear this murmur at times in patients with severe decompensation evidently because of the small blood flow through the valve. After decompensation was corrected, the systolic murmur was clearly heard.

In most cases of aortic stenosis, the systolic murmur is best heard in the second of third right intercostal space at the sternum. In young patients it is sometimes audible with maximum intensity in the third left intercostal space at the sternum or over the heart apex. In such cases it is often mistaken either for the murmur of ventricular septal defect or for the murmur of mitral insufficiency. The presumption of the independent mitral insufficiency seems all the more probable since in aortic stenosis a high-frequency component of the systolic murmur is mainly transmitted to the heart apex, as the result of which the apical murmur is of a higher pitch. It is even musical at times. The true nature of this murmur is easily identified on the phonocardiogram. Although this murmur differs in pitch from the systolic murmur heard over the base of the heart and over the carotid artery, on the phonocardiogram it is not pansystolic as in most cases of mitral insufficiency, but has a spindle shape characteristic of aortic stenosis and begins after the first sound. The typical systolic murmur in supraclavicular aortic stenosis and in patients with pulmonary emphysema is best heard over the neck vessels. It is not transmitted to the heart apex.

The systolic murmur is almost always attended by a thrill which is sometimes clearly felt not only in the second right intercostal space, but also on palpation of the carotid arteries. With the development of heart failure the systolic thrill either diminishes no-

ticeably or disappears completely. Our practice confirmed time and again that in subvalvular aortic stenosis the systolic thrill may be manifested most sharply either over the heart apex or along the left sternal edge. In the latter case it must be differentiated from the systolic thrill heard in ventricular septal defect. In most cases of aortic stenosis a moderately loud fading diastolic murmur is heard in the second-third left intercostal space at the sternum, which starts at the beginning of diastole. In congenital aortic stenosis, aortic insufficiency is mild. Signs of severe aortic insufficiency are evidence of concomitant bacterial endocarditis or aortic stenosis consequent upon rheumatic fever.

The authors of manuals published in past years on cardiology, phonocardiography, and differential diagnosis of internal diseases attached much attention to the character of changes in the heart sounds in aortic stenosis (Friedberg, 1966, Bauer, 1967). Cineangiography conducted in combination with intercardiac phonocardiography showed that the loudness of the second sound is determined by the mobility of the aortic valve cusps.

In the opinion shared by all authors, the first heart sound in aortic stenosis is diminished. In most patients with congenital valvular stenosis an early systolic ejection sound is heard and recorded after the first sound. It is also sometimes detected in cases of hypertrophic cardiomyopathy. The ejection sound is never audible in supravalvular aortic stenosis. Nor is it heard in valvular aortic stenosis in aged patients. The atrial gallop rhythm is audible not only in all types of aortic stenosis, but also in many other diseases. The ventricular gallop rhythm is encountered in all types of aortic stenosis. Its appearance indicates that left-ventricular failure has developed.

Aortic stenosis often leads to very mild changes in the size and configuration of the heart and the ascending aorta. Even in severe stenosis the heart is only slightly enlarged at the expense of left-ventricular hypertrophy. Considerable enlargement of the heart is only encountered when aortic stenosis is combined with insufficiency of the valve or when it is complicated by the development of arterial hypertension or heart failure. If mitral heart disease can be ruled out, the severity of aortic stenosis may be quite confidently determined from the size of the left atrium. In valvular stenosis, the ascending aorta is slightly dilated in the middle third. In supravalvular stenosis it does not change, whereas in diffuse hypoplasia of the aorta its transverse dimension is even less than normal. Signs of aortic valve calcification are found in almost all patients over 40 years of age suffering from valvular stenosis of the aorta. In subvalvular and supravalvular aortic stenoses the valve cusps are never calcified.

A normal or hardly changed ECG is encountered in an adult

suffering from aortic stenosis with mild or moderate left-ventricular hypertrophy. In children even severe stenoses of the aorta may not be attended with ECG changes probably because the heart is deviated about its axis and there is insufficient time for the development of marked left-ventricular hypertrophy. Signs of pronounced hypertrophy and excessive loads experienced by the left ventricle testify not only to acquired severe stenosis but also to ischaemia and scarring in the subendocardial areas of the left ventricle.

Thus, the main signs of the syndrome are the following: a loud systolic murmur over the aorta with radiation of its low-frequency component to the carotid arteries and its high-frequency component to the heart apex, and localized dilatation of the ascending aorta. Diagnostic difficulties are experienced in the initial stage of the stenosis because these signs are insufficiently clear, and in the far-advanced stages because heart failure develops in attendance. The systolic murmur completely disappears in severe heart failure. The severity of aortic stenosis may be judged from the shape and duration of this murmur only if there is no heart failure. The severity of the stenosis undoubtedly determines the shape and volume of the pulse in the peripheral arteries, but heart failure may noticeably reduce the pulse volume and, consequently, its shape. Paradoxical splitting of the second heart sound seems to be the only sign which is determined by the extent of the stenosis itself and not by the severity of the heart failure complicating the stenosis.

The severity of aortic stenosis may be judged by the size of the left ventricle, but this rule is not applicable to aortic stenosis of atherosclerotic origin. The size of the left ventricle in persons of elderly and old age is determined not only by the severity of aortic stenosis, but also by the degree of coronary atherosclerosis. In appraising the signs discussed above it should be borne in mind that left-ventricular failure itself develops under the effect of aortic stenosis and its appearance, therefore, testifies to the severity of the stenosis.

A loud systolic murmur over the base of the heart is encountered in aortic stenosis, pulmonary stenosis, aortitis and acute mitral insufficiency. This murmur is often attended with a thrill which, in aortic stenosis, is transmitted to the right subclavian and carotid arteries. The systolic murmur of pulmonary stenosis is audible on the left side of the neck. It is not transmitted to the right subclavian artery. Aortic stenosis develops in association with hypertrophy of the left, and pulmonary stenosis with hypertrophy of the right ventricle. The electrocardiographic signs of hypertrophy of the corresponding ventricle make it far easier to identify the cause of the systolic murmur. Moreover, the *QRS* complex in lead V_{1-3} is often changed in pulmonary stenosis but not in aortic stenosis. X-ray examination demonstrates localized (poststenotic) dilatation

of the ascending aorta in aortic stenosis and poststenotic dilatation of the right and left pulmonary arteries in pulmonary stenosis. Dilatation of the left pulmonary artery is especially characteristic.

The systolic murmur audible in acute mitral insufficiency is indistinguishable from the systolic murmur of aortic stenosis. The final diagnosis is based on the information gained from the medical history, the comparison of the size of different heart cavities, and the patterns of the course taken by the disease. Aortic stenosis is a chronic disease and the signs of left-ventricular failure develop gradually in it, usually becoming obvious 20 to 30 years after the onset of the disease. Acute mitral insufficiency develops turbulently. The patient seeks the doctor's advice because of attacks of paroxysmal dyspnoea which occur suddenly following one another in rapid succession. The patient usually knows nothing of his heart disease and learns of the systolic murmur for the first time from his doctor. Localized dilatation of the ascending aorta is a constant sign of aortic stenosis but is not encountered in acute mitral insufficiency.

In some cases of aortic stenosis, the systolic murmur is much louder over the apex than over the base of the heart. When it is only heard over the apex, it is hard to differentiate it from the murmur of mitral insufficiency. A sinus heart rhythm, moderate enlargement of the left ventricle and good tolerance of physical exertion at young age are equally characteristic of patients with aortic stenosis and of those suffering from isolated mitral insufficiency. The diseases differ in the further courses. Pain in the heart and syncope develop with time in aortic stenosis, and palpitation, extrasystoles and cardiac fibrillation in mitral insufficiency. Comparison of the results of the auscultative and phonocardiographic findings with the size of the left atrium and left ventricle may yield important information for making the differential diagnosis. The left heart cavities are enlarged early in mitral insufficiency, whereas in aortic stenosis they are normal in size for a long time. The first heart sound retains its pitch in aortic stenosis, but it is usually diminished and sometimes even inaudible in mitral insufficiency. The systolic murmur begins some time after the first sound in aortic stenosis, but immediately after it in mitral insufficiency. The ascending aorta may be dilated only in aortic stenosis. The pain syndrome usually develops in attendance to left-ventricular failure in mitral insufficiency whereas in aortic stenosis it appears long before heart failure develops. In cases presenting a diagnostic problem, catheterization of the heart must be resorted to, during which the pressure gradient through the aortic valve and the character of blood pressure changes in the left atrium during the cardiac cycle are determined.

The systolic murmur of aortic stenosis is easily distinguished

from innocent murmurs audible in the second right intercostal space. A supraclavicular or carotid murmur which may radiate downward to the second right or left intercostal space is often encountered in childhood and adolescence. It is best heard above the clavicle next to the base of the sternocleidomastoid muscle. The supraclavicular murmur occupies about half of systole and is not attended by a thrill.

In atherosclerosis of the aorta, the systolic murmur may be short or long. Sometimes it is attended by a thrill and at other times it is preceded by the ejection sound. In aged and elderly individuals this murmur often radiates to the heart apex. In all cases it does not reach the beginning of the second sound aortic component on the phonocardiogram. The elderly age of the patient in combination with signs of atherosclerotic involvement of other organs allows the true cause of this murmur to be identified. A systolic and often continuous murmur in panaortitis with involvement of the orifices of the great vessels of the aortic arch and in coarctation of the aorta may be very loud and accompanied with a thrill. The ascending aorta may be dilated. Concomitant lesions of other organs and the unusual development of collateral circulation make it easy to differentiate these diseases from aortic stenosis.

A **systolic murmur in the second left intercostal space** is particularly common in childhood and adolescence. It is an innocent murmur in most cases. An organic systolic murmur in this region is caused by **pulmonary stenosis** which may be localized on the level of the valves, in the right ventricle, in the pulmonary trunk or in its branches. The main signs of pulmonary stenosis on the valvular level are dilatation of the pulmonary artery, a systolic murmur, characteristic changes in the ECG and heart sounds and enlargement of the right ventricle. Physical examination discloses a systolic murmur often with a systolic thrill, elevating pulsation of the right ventricle best seen at the left sternal edge in the second or third intercostal space, a diminished percussion sound over the lower third of the sternum, and strong pulsation of the right ventricle in the epigastrium.

In pulmonary stenosis, the first heart sound does not change in intensity. In most cases it is accompanied by the ejection sound heard best in the second left intercostal space. It become softer on inspiration and louder on expiration and is never transmitted to the heart apex or to the carotids. The duration of the interval between the first sound and the ejection sound is determined by the severity of the stenosis. The severer the stenosis, the shorter the interval. In mild stenosis both sounds are separated by an interval percepted by ear. In very severe stenosis the ejection sound may practically merge with the first heart sound. The systolic murmur of pulmonary stenosis is best heard in the second intercostal space

at the sternal edge. Its intensity grows by the end of systole. In some instances it is best heard in the third intercostal space. The murmur and thrill radiate upward and to the left. Sometimes they are well detected on the left side of the neck. The severer the stenosis, the longer is the murmur. A diamond-shaped, more or less symmetric systolic murmur beginning from the ejection sound and ending before the aortic component of the second sound is evidence of mild valvular pulmonary stenosis. A loud systolic murmur with maximum intensity in the late systolic period and ending after the aortic component of the second sound indicates severe pulmonary stenosis.

In pulmonary stenosis, the right ventricle is hypertrophic and the degree of its hypertrophy correlates well with the level of systolic pressure in its cavity. Analysis of the ECG makes it possible to appraise the severity of pure pulmonary stenosis quite accurately. The heart maintains a sinus rhythm in most cases of pulmonary stenosis. Cardiac fibrillation develops only in very severe stenosis marked by considerable distension of the right atrium. In mild pulmonary stenosis, the dimensions of the heart do not change, only a small bulging of the pulmonary artery conus is noted. In severe stenosis the pulmonary trunk is dilated. A faded pulmonary pattern is only encountered in severe pulmonary stenosis. Post-stenotic dilatation of the left pulmonary artery, which often forms an additional protrusion on the left heart contour, is always seen in valvular pulmonary stenosis. In **infundibular stenosis** the left border of the heart shadow is usually straight or even concave. In unilateral stenosis of the right and left pulmonary arteries, the vascular pattern of one lung differs sharply from that of the other.

X-ray does not always disclose hypertrophy of the right ventricle, whereas in cases of its dilatation the question always arises whether it is caused by heart failure or by excessive loading of the right ventricle with blood entering it from the left heart through a shunt on a level with the atria or ventricles. To answer this question one often has to resort to special methods of examination among which catheterization of the right heart cavities and angiography are of foremost importance. Catheterization of the heart allows measurement of the pressure gradient between the right ventricle and the pulmonary artery. Valvular pulmonary stenosis is characterized by sharp increase of systolic and drop of diastolic pressure at the moment the catheter is withdrawn from the pulmonary artery into the right ventricle. In subvalvular stenosis, only the diastolic pressure drops when the catheter is in the infundibular chamber of the right ventricle. The systolic pressure does not change meanwhile. A sharp rise of arterial pressure occurs only at the moment when the catheter enters the main cavity of the right ventricle. Selective angiography demonstrates post-stenotic bulging of the

pulmonary trunk and a slower than normal contrasting of its peripheral branches.

Supravalvular pulmonary stenosis may be reliably diagnosed only by means of selective angiography with injection of the contrast medium into the right ventricle or the pulmonary artery. The angiocardiogram usually shows prestenotic and post-stenotic dilatation of the pulmonary artery branches and not the site of their constriction.

Atrial septal defect is encountered both as an isolated disease and in combination with other developmental anomalies. If the defect is small and the only developmental anomaly, it may produce absolutely no clinical manifestations till the person is 30 to 40 years old. Persons with this defect often regard themselves healthy and engage in physical labour, often learning for the first time of their anomaly from a doctor examining them because of some other disease. This circumstance clearly explains why an atrial septal defect is encountered in departments for adults with internal diseases much more frequently than all the other congenital heart diseases.

Small defects are often aphonic. This is encountered especially often in children of kindergarten age. The systolic murmur of atrial septal defect is frequently mistaken for an innocent murmur and only scrupulous questioning of the mother sometimes divulges that the child had been cyanotic for several days during one of the particularly severe attacks of pneumonia. Short-term cyanosis may develop for the first time in adults only during extraordinary physical exertion. In one of our female patients it appeared for the first time during delivery.

The systolic murmur in atrial septal defect begins immediately after the first sound. The phonocardiogram shows that it is spindle-shaped and ends before the second sound begins. It is usually soft and with no attendant thrill. Its maximum intensity is in the second left intercostal space. Sometimes the murmur radiates to the heart apex, usually no further than the fourth intercostal space. Intracardiac phonocardiography establishes that this murmur is of pure haemodynamic origin and arises in the dilated pulmonary artery. Passage of blood through the defect in the interatrial septum does not induce any murmur. The systolic murmur in atrial septal defect never obscures the aortic component of the second heart sound.

The shunt of blood from the left into the right atrium leads to an increase in the volumetric blood flow rate through the tricuspid valve. This results in the origin of a diastolic murmur which occupies the middle of diastole in typical cases. The first heart sound may be split. An ejection sound is recorded on the phonocardiogram in approximately 50 per cent of cases. It occurs because the pul-

monary trunk is distended and is only heard over the base of the heart. It is not transmitted to the heart apex.

Particular diagnostic significance is attached to the character of changes in the second heart sound. Fixed splitting of the second sound and a systolic murmur are the main diagnostic signs of atrial septal defect. They are encountered in every case of this disease but only till a functioning shunt exists. The development of right-ventricular failure changes the conditions of intracardiac circulation, as a consequence of which the auscultative picture of the disease changes. Progressive increase in the volume of residual blood in the right ventricle leads first to its hypertrophy and eventually to its dilatation. Relative tricuspid insufficiency develops. Blood pressure in the right atrium rises gradually and becomes equal to that in the left atrium. The atrial shunt ceases functioning. The appearance of cyanosis indicates that the pressure has become higher in the right than in the left atrium. Right-ventricular dilatation is attended by a pansystolic murmur which is heard clearly over the heart apex because the apex is formed by the right ventricle. This pansystolic murmur of tricuspid insufficiency is often misdiagnosed as the pansystolic murmur of mitral insufficiency. Dilatation of the right ventricle in conjunction with an increased blood flow through the right heart creates conditions for the origin of the third heart sound which is best heard in the third or fourth left intercostal space at the sternal edge. Pulsation of the right ventricle is also best revealed here. High pulmonary hypertension may lead to the appearance of the diastolic Graham Steell murmur.

The differential diagnosis between atrial septal defect and mitral stenosis is made easier if the patterns in their clinical course are compared with the results of X-ray examination. Marked, often aneurysmatic, dilatation of the pulmonary trunk and particularly the right pulmonary artery is the principal X-ray sign of atrial septal defect. The left pulmonary artery is also dilated, but it is obscured by the distended pulmonary trunk. Congestion of the lungs is particularly noticeable in young patients. With the development of pulmonary hypertension, the signs of increased blood flow through the lungs are less manifest. In some cases they are even undetected. The aorta always seems small and its bulging is often not demonstrated at all. The dimensions of the left ventricle are always normal. These X-ray signs are always encountered only in atrial septal defect with a considerable blood shunt. In cases with a small defect the X-ray picture of the heart and lungs may be normal.

The characteristic ECG changes often help in the diagnosis of atrial septal defect or allow it to be suspected. The sinus heart rhythm usually lasts to the age of 30. Extrasystoles and short paroxysms of cardiac fibrillation or paroxysmal tachycardia appear

later. Permanent cardiac arrhythmia is found in all patients after the age of 40. The gradual distension of the atrium is attended by a high *P* wave on the ECG whose height exceeds 2.5 mm in leads II, III and aVF and 1.0 mm in lead V_1. Intravenous angiocardiography demonstrates enlargement of the right heart cavities and pulmonary artery. The 'washing out' of the contrast medium from the right atrium and its repeated contrasting from the left atrium are regarded to be a characteristic symptom. During catheterization of the heart the catheter is advanced from the right atrium directly into the left atrium, which is authentic evidence of an anatomical defect in the septum.

A systolic murmur with maximum intensity in the second left intercostal space is a characteristic sign of **ventricular septal defect.** Congenital defects in the septum are far more common than acquired defects. They may be isolated or combined with other developmental anomalies of the heart and large vessels. Approximately 10 per cent of defects in the interventricular septum are localized above the muscular ridge. The systolic murmur of this defect is best heard in the second left intercostal space. About 70 per cent of all ventricular septal defects are localized behind the muscular ridge. The diameter of this defect ranges from 1 to 3 cm. Defects of medium size lead to mild pulmonary hypervolaemia. Infants with such a defect gain weight slowly and often suffer from acute respiratory infections. After the age of two or three years the child grows stronger and develops normally. Large ventricular septal defects are complicated early by heart failure.

The localization and pronounced character of the systolic thrill are determined by the localization and size of the defect in the interventricular septum. No thrill may be heard when the defects are very small. If the defect is above the ventricular ridge, the blood stream from the shunt is directed into the pulmonary trunk. The systolic murmur and thrill in such cases are clearer in the second left intercostal space and may even be transmitted to the neck. Depending on the volume of the shunt they resemble either a systolic murmur or a systolic murmur and thrill characteristic of pulmonary stenosis. In a defect localized below the muscular ridge, the maximum intensity of the murmur is shifted to the third or fourth intercostal space. Its duration and loudness are determined by the pressure gradient between the ventricles during systole.

In small ventricular septal defects the systolic murmur is usually of a fading character and is clearly heard in the third or fourth intercostal space. It occupies the beginning of systole and ceases in the middle because contraction of the ventricles in the late phase of systole disrupts the functioning of the shunt. A pansystolic murmur is testimony of a large defect in the interventricular septum. With the development of pulmonary hypertension the pressure

gradient between the left and right ventricles gradually decreases. When the pressure in the left ventricle equals that in the right, the shunt disappears. Only signs of pulmonary hypertension remain. The systolic murmur of ventricular septal defect may be noticeably intensified or diminished by increasing or reducing the pressure gradient between the ventricles. The systolic murmur is intensified by phenylephrine hydrochloride and weakened by amyl nitrite. The normal respiratory splitting of the second sound is preserved only when the defect is small. If Eisenmenger's syndrome develops, the second heart sound becomes loud and is always formed by a sole component. This is explained by simultaneous closure of the aortic and pulmonary valves because in this syndrome the ventricles communicate extensively, whereas blood pressure in the aorta is the same as that in the pulmonary artery.

The diastolic murmur in ventricular septal defect is encountered in two variants. In some cases the blowing diastolic murmur is caused by distension of the pulmonary orifice. In others it is a consequence of increased blood flow through the mitral valve. The murmur of pulmonary insufficiency arises at the beginning of diastole. It is transmitted along the left sternal edge in the third or fourth intercostal space. It has to be differentiated sometimes from the diastolic murmur of aortic insufficiency. The absence of peripheral signs of aortic insufficiency is its principal differential diagnostic sign. The volume of blood flowing through the mitral valve in large defects in the interventricular septum sometimes leads to the origin of a murmur which is best heard in mid-diastole. The phonocardiogram shows that this mesodiastolic murmur precedes the third heart sound but does not begin from it as the case is with myocarditis and cardiomyopathy.

The X-ray signs of the disease depend on the volume of blood shunted through the opening in the interventricular septum. The size and shape of the heart do not change when the defects are small; in defects of average size the heart is enlarged at the expense of both ventricles and the left atrium. The higher the pressure in the pulmonary artery, the more sharply its conus protrudes. Pulsation of the pulmonary roots is sometimes noted. The peripheral parts of the lungs are abnormally transparent because the peripheral branchings of the pulmonary artery are insufficiently pronounced. Angiography reveals signs of pulmonary hypertension and repeated contrasting of the right ventricle and pulmonary artery in left-to-right shunt. Selective angiography with injection of the contrast medium into the left atrium or left ventricle often demonstrates simultaneous contrasting of both ventricles. ECG changes in ventricular septal defect have no high differential diagnostic significance.

A systolic murmur in the second left intercostal space is one of

the constant signs of **persistent ductus arteriosus.** Cases of this disease differ sharply from one another in the course, character of complications, and clarity of physical signs. Patients with a diameter of the ductus of just a few millimeters are in no way outwardly different from healthy individuals. An extraordinary murmur in the precordial region may be the only abnormality found on physical examination of these patients. The classical murmur of non-complicated persistent ductus arteriosus reaches maximum in late systole, continues uninterruptedly beyond the second heart sound and obscures it, and gradually diminishes in intensity during diastole. The murmur may be audible throughout the cardiac cycle. It is usually absent at the end of diastole but sometimes it may also be inaudible at the onset of systole. Its maximum intensity on auscultation is usually determined in the second or first left intercostal space, in rare cases in the third left intercostal space. The systolic component of the murmur is also audible between the scapulae as a rule. A third sound is often heard over the heart apex in children, from which a short mesodiastolic murmur begins. It is caused by increased blood flow through the left heart cavities. When the diameter of ductus arteriosus is small, the ECG is normal.

Patients suffering from persistent ductus arteriosus of a large diameter develop more slowly physically than healthy children of the same age and suffer from shortness of breath. The increased flow of blood through the left heart cavities leads to distension of the left atrium and left ventricle. The heart beat is exaggerated. Cardiac fibrillation develops in considerable distension of the left atrium. With the gradual increase in pressure in the pulmonary artery, the diastolic component of the continuous murmur becomes shorter and the diastolic murmur finally disappears completely. Only a pansystolic murmur is audible.

If pulmonary hypertension continues growing, the systolic murmur also becomes shorter and disappears when blood pressure in the pulmonary artery exceeds the pressure in the aorta. Persistent ductus arteriosus becomes aphonic. Instead of a continuous murmur an ejection sound appears in a patient who has signs of marked pulmonary hypertension. It arises in the pulmonary artery and is followed by a short mesodiastolic murmur. The second heart sound is accentuated because its pulmonary component intensifies. Entry of venous blood into the aorta distal to the great vessels of the aortic arch sometimes leads to the development of discrete cyanosis.

The appearance of the diastolic murmur is evidence of pulmonary insufficiency resulting from distension of the fibrous ring of the pulmonary artery. A soft diastolic murmur of pulmonary insufficiency is best heard in the second intercostal space at the left

sternal edge. It is usually transmitted to the third left intercostal space. The diagnosis of persistent ductus arteriosus cannot be established from the findings of auscultation at this stage of the disease. The pronounced character of the X-ray signs of the disease is mainly determined by the severity of pulmonary hypertension. Repeated contrasting of the pulmonary artery with blood entering from the aorta or repeated entry of the radioisotope into the pulmonary artery is a very valuable indirect sign of a functioning ductus arteriosus. Aortography or ventriculography is resorted to when the diagnosis causes doubt. The contrast medium is introduced into the base of the aorta in the first case, and into the left ventricle in the second. The aorta, the pulmonary artery and, in some cases, the ductus arteriosus are also extensively contrasted by means of this method. The ECG changes in persistent ductus arteriosus have no independent diagnostic significance.

A systolic murmur is always heard in the second left intercostal space in **idiopathic dilatation of the pulmonary artery.** The principal diagnostic criteria of this condition are as follows: pulsation of the pulmonary artery in the second left intercostal space, a short systolic murmur beginning from the pulmonary ejection sound, normal respiratory splitting of the second heart sound, and bulging of the conus of the pulmonary artery on the radiograph. The diagnosis of idiopathic pulmonary artery dilatation may only be made if the patient has no signs of pulmonary hypertension, pulmonary congestion or signs of right-ventricular hypertrophy.

Pulmonary hypertension of any origin may be accompanied with a systolic murmur best heard in the second left intercostal space. The murmur often begins from a high-frequency ejection sound and has a spindle-shaped configuration with maximum oscillation amplitude in midsystole. The ejection sound, just as the systolic murmur, radiates along the left sternal edge usually to the third and very rarely to the fourth intercostal space. The systolic murmur is a secondary sign of pulmonary hypertension and the differential diagnosis of this disease is therefore discussed in detail in the section dealing with right-ventricular failure.

A systolic murmur in the second left intercostal space also arises in **accelerated flow of blood in the pulmonary artery.** This is encountered in anaemia, thyrotoxicosis, pregnancy, arteriovenous aneurysms, fever and physical exertion. This murmur is also audible in adolescents, boys and girls, of asthenic build with no signs of any disease of the internal organs. The murmur is always short, blowing, it is never attended with a thrill and is not transmitted to the neck arteries. The haemodynamic origin of the systolic murmur in the hyperkinetic syndrome leaves no room for doubt. The cause of its origin in other cases is still unknown.

Diastolic Murmur

Diastolic murmurs are localized between the second and first sounds of the cardiac cycle. They may occupy entire diastole or only part of it. The following three main causes of their origin are distinguished: deformity of the valve cusps, dilatation of the fibrous valvular ring, and increased volumetric rate of blood flow through the valve. The murmurs of aortic and pulmonary insufficiency arise at the very beginning of diastole. Late diastolic murmurs are usually called presystolic. Functional murmurs are localized in mid-diastole.

Early diastolic murmurs begin immediately after the second heart sound. A model of such murmurs is the murmur of *aortic insufficiency*, a clinical syndrome occurring as the result of incomplete separation of the aorta and left ventricle during diastole. The diastolic murmur is a constant and, in many cases, the only sign of aortic insufficiency. The diagnosis of this disease may be established in most cases on the basis of the results of physical examination alone. The apex beat is exaggerated in mild aortic insufficiency, but is diffuse and is displaced to the left and downward to the sixth and even seventh intercostal space in severe insufficiency.

Arterial pressure in mild aortic insufficiency is normal. In severe aortic insufficiency, the diastolic pressure drops to 60 and even to 40-30 mm Hg, whereas the systolic pressure rises to 170-220 mm Hg. In severe aortic insufficiency only the systolic arterial pressure may be measured by Korotkov's method. The level of the diastolic arterial pressure cannot be determined by this method because a continuous arterial sound appears which is audible over the brachial artery even when the air is completely pressed out of the cuff. An abrupt and rapid pulse, carotid shudder, movement of the head synchronous with the heart beat (*de Musset's sign*), 'capillary pulse' (*Quincke's pulse*), extraordinarily warm skin and *Duroziez's murmur* had long been regarded as signs of severe aortic insufficiency. They are now generally included among the nonspecific signs of the hyperkinetic syndrome developing in many diseases. They are in no contradiction to the diagnosis, but nor do they confirm it.

The first heart sound in aortic insufficiency is noticeably diminished. In severe cases it is inaudible. The ejection sound is best heard at the heart apex. On auscultation it is mistaken for the splitting of the first sound. In diseases of the aortic root complicated by aortic insufficiency, the second heart sound is usually intensified, whereas in lesion of the semilunar valves, it is diminished. The diastolic murmur is a *conditio sine qua non* of the diagnosis of aortic insufficiency. A systolic and presystolic murmurs are heard in the

precordial region in addition to the diastolic murmur in some cases of aortic insufficiency. The murmur of aortic insufficiency is usually best heard in the third intercostal space. The zone of its maximum intensity is sometimes shifted to the first right intercostal space and sometimes to the heart apex.

The duration of the murmur is determined by the severity of aortic insufficiency. In mild cases a short diastolic murmur is heard only in a very quiet room. The pulse pressure does not change. A blowing diastolic murmur in moderately severe aortic insufficiency lasts during one half to two thirds of diastole. In severe aortic insufficiency the murmur is heard throughout diastole. The systolic arterial pressure increases in such cases, while the diastolic pressure decreases.

Identification of optimum intensity of the diastolic murmur is of high differential diagnostic significance. Particular importance is attached to the results of comparing the intensity of the diastolic murmur in the third intercostal space at the left and right sternal edges. Murmurs of valvular origin are best heard in the third intercostal space at the left sternal edge, while murmurs of aortic insufficiency resulting from a disease of the aortic root are best heard in the third intercostal space, but only at the right sternal edge. Musical murmurs are encountered in spontaneous or traumatic ruptures of the valve, bacterial endocarditis, syphilitic aortitis and rarely in rheumatic fever.

A systolic murmur is audible in the second right intercostal space in most cases of aortic insufficiency. It arises because of increased volumetric rate of blood flow through the deformed aortic valve, i.e. it is one of the haemodynamic signs of the hyperkinetic syndrome. It may even be accompanied with a systolic thrill.

The diastolic murmur in severe aortic insufficiency is sometimes marked by presystolic intensification (*Flint's murmur*). Analysis of the following signs allows it to be distinguished from the presystolic murmur of mitral stenosis. An aortic shape of the heart with enlargement of the left ventricle is typical of aortic insufficiency, whereas a mitral shape of the heart with X-ray and electrocardiographic signs of right-ventricular hypertrophy is characteristic of mitral stenosis. The detection of these signs indicates the probable association of the presystolic murmur with either of these heart diseases. The opening snap of the mitral valve is evidence in favour of the presystolic murmur of mitral stenosis, but its absence does not rule out the diagnosis of this disease. Enlargement of the left atrium and pulmonary hypertension are common signs of mitral stenosis. In cases of aortic insufficiency they are encountered only if the condition is complicated by left-ventricular failure. Severe and long-existing pulmonary hypertension signifies that the presystolic murmur is associated with mitral stenosis. By lowering

the blood pressure in the aorta amyl nitrite causes diminution and even disappearance of Flint's murmur. The presystolic murmur of mitral stenosis is often intensified after prescription of amyl nitrite.

The diastolic murmur of aortic insufficiency and that of pulmonary insufficiency are identical in the mechanism of their origin and in the auscultative signs. They can be distinguished from each other only by signs attendant to the characteristic murmur. The diastolic murmur of aortic insufficiency is best heard at the edge of the sternum in the second right intercostal space or in the third or fourth left intercostal space. The diastolic murmur of pulmonary insufficiency is transmitted along the left sternal edge as a rule. It is audible in the second right intercostal space only in cases of very severe pulmonary hypertension. The loud and continuous diastolic murmur of aortic insufficiency is always combined with a large pulse pressure and with a low or very low diastolic blood pressure in the brachial artery. Such changes in blood pressure are not encountered in pulmonary insufficiency. These syndromes may be easily distinguished from each other by aortography.

Pulmonary insufficiency may be congenital or acquired. A continuous fading diastolic murmur is its principal sign. The murmur is best heard in the second or third left intercostal space. In some cases, but not always, it is noticeably louder during inspiration. The diastolic murmur of pulmonary insufficiency in a patient with mitral stenosis and pulmonary hypertension was described for the first time by Still who determined the principal diagnostic criteria of this murmur, namely, a soft blowing character and its beginning from an accentuated second heart sound. Still also noted that in cases of splitting of the second sound, the murmur he had described begins from the second component. The diastolic murmur of relative pulmonary insufficiency is encountered in pulmonary fibrosis of various origin, persistent ductus arteriosus, atrial and ventricular septal defects and other diseases complicated by pulmonary hypertension.

Late diastolic (presystolic) murmurs are usually produced in *mitral stenosis* which, as a rule, is of rheumatic origin. Congenital mitral stenosis is an extremely rare disease. Its clinical picture is fully displayed in the first months of the infant's life and therefore cannot be misdiagnosed as mitral disease of rheumatic origin. Narrowing of the left atrioventricular orifice with short-lived complete obturation is sometimes caused by a *thrombus* or *myxoma of the left atrium*. The intensity of the murmur is determined by the rate of the blood flow through the valves and has two maximums: one at the beginning and the second at the end of diastole. A murmur audible throughout diastole is louder at the beginning and at the end. It is sometimes divided into two components. The first begins imme-

diately after opening of the mitral valve, while the second coincides in time with atrial systole. The protodiastolic component of the murmur has a diminishing and the presystolic (atrial) component an intensifying character. In some cases only a presystolic murmur reflecting intensification of the blood flow through the valves under the effect of left atrial systole is audible.

A continuous musical diastolic murmur with presystolic intensification and attended by a thrill ('cat's purr') is one of the most reliable physical signs of mitral stenosis. Presystolic intensification of the murmur is sometimes detected only after physical exercise accelerating the blood flow through the mitral valve. A presystolic murmur, or, to be more precise, presystolic intensification of the diastolic murmur, disappears completely with the development of cardiac fibrillation marked by arrest of left atrial contractile function. Diminished contractile function of the left atrium may also lead to the disappearance of the diastolic murmur. The diastolic mitral murmur is audible over a restricted chest area in most cases. Sometimes it is heard only at one point. The apex beat proves to be such a point most frequently. Sometimes it is audible only when the patient lies on his left side and the apex of the left ventricle comes closer to the chest wall.

The diastolic murmur results not only from the turbulence of the blood stream, but also from the fluctuation of the valve structures. A calcified valve loses its capacity of fluctuation under the effect of flowing blood sharply or even completely. Consequently, the diastolic murmur diminishes or disappears. The opening snap also disappears simultaneously. Shortening of the chordae tendineae leads to restriction of the mobility of the valve cusps because they are drawn into the left-ventricular cavity. As a result, the opening snap disappears and the diastolic murmur diminishes or even also disappears. Thrombosis of the left atrium is often accompanied with diminution and sometimes even disappearance of the diastolic murmur. Tachycardia makes it very difficult to detect the diastolic murmur.

The diastolic murmur of mitral stenosis is often encountered at the same time as the systolic murmur which is sometimes the only murmur of isolated mitral stenosis. The origin of this murmur may be attributed to calcification and rigidity of the mitral valve cusps and concomitant mitral or tricuspid insufficiency. Mitral stenosis is attended by characteristic changes in the heart sounds. The first sound alters particularly sharply. It becomes short and loud (flapping). In no other heart disease is the first sound so loud. The flapping character of the first sound is also preserved in tachycardia. Intensification of the first sound is of diagnostic significance only if encountered simultaneously with the characteristic murmur described above.

The second heart sound in mitral stenosis is usually intensified and sometimes also split. Its second component is always recorded before the *opening snap*. In a healthy person the mitral valve cusps open soundlessly 0.07-0.10 second after the second heart sound. When these cusps are sclerosed, their fluctuations at the beginning of diastole are attended by the opening snap of the mitral valve heard both over the base and over the apex of the heart, whereas splitting of the second sound is best heard over the base of the heart. The opening snap does not depend on the respiratory phases. It is audible during inspiration and expiration and is attended by a diastolic murmur in both cases. Respiratory splitting of the second sound is usually heard only on inspiration, during expiration both components of the split second sound merge into a single sound.

Combination of the three heart sounds with a diastolic murmur produces a characteristic melody encountered only in mitral stenosis. A triple rhythm is not a constant sign of mitral stenosis. It is often absent in mild or in far advanced stenosis. The opening snap (as the diastolic murmur) is sharply diminished and may disappear in calcification of the valve cusps or in their rigidity caused by shortening of the chordae tendineae or sclerosis of the papillary muscles.

A diastolic murmur heard in the precordial region is one of the main signs of *tricuspid stenosis*. In most cases it is intensified at the peak of inspiration. This happens only in cases of tricuspid disease with a maintained sinus rhythm and only in patients with sufficient reserve of heart contractile function. The characteristic diastolic murmur of tricuspid stenosis is best heard over the lower third of the sternum as well as in the fourth and fifth intercostal spaces between the left sternal edge and the heart apex. Marked hypertrophy of the right ventricle is attended with displacement of the heart about its long axis as a result of which the right ventricle may even form the border. The diastolic murmur of tricuspid stenosis in such cases is best heard over the heart apex where it may be mistaken for the murmur of mitral stenosis.

Mesodiastolic murmurs. Mitral insufficiency is often complicated by a diastolic murmur which begins from the third sound and ends before the beginning of the first sound. A silent interval is always detected between the second sound and the beginning of the murmur. The third heart sound precedes the murmur in many but not in all cases. The intensity of the murmur is determined by the volumetric rate of the blood flow through the valve and by the duration of diastole. The variable loudness of the murmur in one and the same patient is particularly evident in cardiac fibrillation. The longer the diastolic pause of the heart, the louder is this mur-

mur. On repeated auscultation of this murmur in one and the same patient, changes may be detected in its intensity depending on the patient's condition. Dilatation of the left ventricle in its failure is accompanied with intensification of the mesodiastolic murmur. When heart failure is corrected and the heart grows smaller, the murmur disappears. With deterioration in the patient's condition, it may reappear. Follow-up of this mesodiastolic murmur in mitral insufficiency provides grounds for the assumption that left-ventricular dilatation is among the causes of its origin.

Thus, clinical experience makes it possible to distinguish and appraise separately two principal causes of the mesodiastolic murmur in pure mitral insufficiency: increased volumetric rate of blood flow through the valve and changed myocardial contractility the indirect reflection of which are fluctuations in the size of the left ventricle. The first of these causes plays a prominent role in the origin of the diastolic murmur in hyperkinetic states, whereas the second determines to a great measure the intensity of this murmur.

The main difficulty of auscultation consists in the fact that some of the diseases listed in Supplement XV-4 are attended by murmurs which occupy the middle of diastole in some cases or are audible only before the beginning of systole in others. Myxoma and spherical thrombus of the atrium are examples of such diseases. Migration of the diastolic murmur from mid-diastole to presystole very often perplexed us in cases of atrial thrombi. Spherical or pedicle thrombi are usually encountered when the principal disease is complicated by cardiac fibrillation. The following features distinguishing the diastolic murmur of mitral stenosis from diastolic murmurs in spherical thrombus and myxoma of the atrium may be pointed out.

The characteristic murmur of mitral stenosis is usually audible throughout diastole and intensifies at the end of it. In some cases, however, it is heard at the beginning and at the end and, at times, only at the end of diastole. Presystolic intensification of the diastolic murmur disappears in cardiac fibrillation, but in such cases too the diastolic murmur is always audible in one and the same stretch of every cardiac cycle. In myxoma or spherical thrombus of the atrium the diastolic murmur is misdiagnosed as mesodiastolic during some cardiac cycles and as presystolic during others. In mitral stenosis, the diastolic murmur does not migrate from one to another stretch of the cardiac cycle. A change in the patient's position, auscultation when sitting or lying down leads simply to diminution or intensification of the characteristic diastolic murmur in mitral stenosis. These manipulations in myxoma or spherical thrombus of the atrium not only change the intensity of the murmur, but

sometimes lead to disappearance of the diastolic murmur, at times to the replacement of the mesodiastolic murmur by a presystolic murmur or vice versa. The inconstancy of the diastolic murmur is a characteristic sign of spherical thrombus and myxoma of the atrium. In mitral stenosis, the diastolic murmur is also inconstant. It is sometimes inaudible in severe heart failure and in severe pulmonary hypertension. In each of these complications of mitral stenosis the diastolic murmur disappears for a long time. In atrial spherical thrombus and myxoma the diastolic murmur may disappear and reappear within the short time that the patient is examined.

A presystolic murmur is sometimes audible over the heart apex in patients with an intact mitral valve. This murmur was described for the first time by Flint in a patient suffering from isolated aortic insufficiency. Any apical presystolic murmur simulating the presystolic murmur of mitral stenosis is currently called Flint's murmur. Flint's murmur is diagnosed only if all other signs of mitral stenosis are absent.

A diastolic murmur is sometimes heard over the heart apex in left-ventricular aneurysm. The origin of this murmur is associated either with left-ventricular dilatation and the formation of relative mitral stenosis or with the entry of blood into the ventricle from the aneurysmatic sac.

A sharp elevation of arterial pressure encountered in hypertensive crisis, for instance, is sometimes attended with a diastolic murmur which persists several days after arterial pressure returns to normal level and then disappears. In our practice these murmurs were of a fading character. Their appearance is generally linked with dilatation of the fibrous ring of the aortic valve. Diastolic murmurs appearing in the terminal stages of malignant arterial hypertension and chronic nephritis are evidently of such origin.

An intracardiac left-to-right shunt at the level of the atria is marked by an increase in the volumetric rate of blood flow only through the tricuspid and pulmonary valves. When the shunt is relatively small, only a systolic murmur over the pulmonary artery is audible. The appearance of a diastolic murmur signifies that the hyperkinetic circulatory condition has led to relative tricuspid stenosis. Similar changes in haemodynamics develop in the left atrioventricular orifice in ventricular septal defect and persistent ductus arteriosus. Diastolic murmurs of functional stenosis of the atrioventricular orifices may not only be mesodiastolic, but also continuous and marked by presystolic intensification characteristic of atrioventricular stenosis.

Supplement XV-1

Classification of Innocent Murmurs

Systolic.
  Extracardiac.
    Cardiopulmonary.
    Vibration (parasternal).
    Supraclavicular (carotid).
    Abdominal.
  Intracardiac.
    Aortic.
    Pulmonary.
Continuous.
  Venous.
  Mammary.

Supplement XV-2

Causes of a Continuous Murmur

Blood shunt.
  Persistent ductus arteriosus.
  Rupture of aneurysm of Valsalva's sinus.
  Coronary arteriovenous aneurysm.
  Arteriovenous aneurysm in pulmonary or systemic circulation.
Arterial stenosis or dilatation.
  Coarctation of the aorta.
  Stenosis and parietal thrombosis of the pulmonary artery.
  Aneurysm of the aorta or pulmonary artery.
  Arteritis of the aorta and its branches.
Increased volumetric rate of blood flow through a vessel.
  Venous hum (murmur).
  Mammary murmur.
  Abdominal murmur.

Supplement XV-3

Causes of a Systolic Murmur

I. Maximum intensity over the heart apex.
  Mitral insufficiency.
    Valvular.
    Subvalvular.
    Mixed.
  Tricuspid insufficiency.
    Valvular.
    Ebstein's disease.
    Mixed.
  Aortic stenosis.
    Valvular.
    Subvalvular.
  Mitral stenosis.
  Innocent murmur.
II. Maximum intensity in the second right intercostal space.
  Aortic stenosis.
  Pulmonary stenosis.

Aortitis.
Atherosclerosis of the aorta.
Acute mitral insufficiency.
Innocent murmur.

III. Maximum intensity in the second left intercostal space.
Pulmonary stenosis.
Atrial septal defect.
Persistent ductus arteriosus.
Idiopathic dilatation of the pulmonary artery.
Innocent murmur.

Supplement XV-4

Classification and Causes of Diastolic Murmurs

Early.
Aortic insufficiency.
Pulmonary insufficiency.

Late.
Mitral stenosis.
Tricuspid stenosis.
Flint's murmur.
Atrial myxoma.
Spherical thrombus of the atrium.

Mesodiastolic.
Ventricular dilatation.
Increased blood flow through the valve.

Chapter XVI

Hepatomegaly and Splenomegaly

The size of the liver is commonly determined by palpation and percussion. Enlargement of the liver may be the predominant or early sign of many diseases. Some of them are marked by isolated hepatomegaly whereas in others the liver and spleen are both enlarged. This chapter provides a systematic description of the differential diagnosis of these diseases.

In appraising the results of palpation of the liver it must be borne in mind that its lower border is always palpated in children and quite often in adults with enteroptosis or marked pulmonary emphysema. Besides the liver, other organs are also palpated in the right hypochondrium and in the epigastrium which are sometimes mistaken for an enlarged liver. During World War II we came across confirmation time and again that an omentum affected by tuberculosis was often mistaken for the liver. Much less frequently tumours of the right kidney, stomach or transverse colon and a distended gall bladder are erroneously recognized as the liver.

The number of diagnostic difficulties is markedly reduced if the rule is observed to appraise, in every single case, the size, consistency and character of the hepatic border along the entire distance accessible to palpation. In heart failure it is soft and slightly tender and is palpated in the right hypochondrium, epigastrium and in the left hypochondrium. In a patient suffering from cirrhosis, the liver may be small, but its border is sharp and firm. It is well known that a rounded and soft border of the liver is found when hydatid cyst grows on its lower surface. Regular palpation of the lower border of the liver makes it possible to distinguish diffuse enlargement of the liver from isolated enlargement of one of its lobes.

Scanning is resorted to when the results of physical examination fail to resolve all doubts regarding the size of the liver. Other methods of its examination will be pointed out whenever necessary. If hepatomegaly is combined with jaundice, it is best to conduct the diagnostic analysis according to the schemes described in the chapter 'Jaundice'.

Acute Anicteric Hepatitis

One of the forms of virus hepatitis, namely, B serum hepatitis or hepatitis with a long-term incubation period, begins insidiously, as a rule, and may develop with no visible jaundice and be manifested only by increased fatiguability and anorexia. Body temperature in such patients is often normal. Examination reveals enlargement of the liver and moderately increased transaminase activity. Moderate enlargement of the spleen is sometimes found. Blood of these patients yields a positive reaction with hepatitis B antigen (HB_sAg, Australia antigen).

Hepatitis B is characterized by a tendency to take a protracted course. Transaminase activity in this form of hepatitis is often increased for many months. It is presumed that precisely B virus hepatitis is the main cause of chronic hepatitis and cirrhosis developing in patients with no history of jaundice who do not abuse alcohol.

Isolated hepatomegaly is also encountered in toxic forms of hepatitis (the differential diagnosis is discussed in the chapter 'Jaundice').

Chronic Hepatitis

Chronic hepatitis is inflammation of the liver continuing uninterruptedly for at least six months. According to the morphological findings, chronic benign (persistent) and aggressive forms of hepatitis are distinguished. Their aetiology has not been fully revealed to date.

According to the findings of intravital biopsy of the liver, chronic benign (persistent) hepatitis is marked by inflammatory infiltration of the portal tract. The lobular structure of the liver is preserved and there is either no fibrosis of the liver or it is very moderate. In aggressive hepatitis, inflammatory infiltration is found both in the portal zones and in the hepatic parenchyma. The lobular structure of the liver is disturbed because foci of hepatic cell necrosis form and connective tissue proliferates within the lobules. These two types of chronic hepatitis develop after acute viral and toxic forms of hepatitis.

Chronic benign (persistent) hepatitis. The morphology of chronic hepatitis was studied in detail by means of intravital biopsy. Comparison of the biopsy findings with the results of long-term comprehensive follow-up of the disease revealed that chronic benign hepatitis is usually consequent upon acute viral hepatitis. It is discovered quite often by chance in donors.

In cases of severer affection, patients complain of constant weakness and rapid fatigue from physical or mental work, of poor tolerance of greasy food, and often of unpleasant sensations in the right hypochondrium. The subjective picture of the disease in such cases is identical with that of the post-hepatic syndrome and asthenic state sometimes developing after acute viral hepatitis. Physical examination reveals mild enlargement of the liver which may be slightly tender. In some cases, physical examination discloses no changes in the internal organs. The assumption that these complaints are associated with a disease of the liver usually arises after the results of special methods of examination are obtained.

The blood bilirubin content may be normal, though mild hyperbilirubinaemia is encountered now and again. Serum transaminase activity is usually slightly increased, sometimes for several years. In chronic benign hepatitis, just as in other diffuse affections of the liver, the alkaline phosphatase activity does not change. A small increase in the content of immunoglobulins in serum is regarded a characteristic sign. The total blood globulin content stays normal (Sherlock, 1976). Serum tests for the content of hepatitis B or hepatitis A antigen sometimes allow the aetiology of hepatitis to be identified. The final diagnosis is established from the results of liver biopsy which should be undertaken no earlier than six months or, still better, twelve months after acute hepatitis had been suffered.

Chronic benign hepatitis has to be distinguished from the post-hepatitic syndrome, post-hepatitic hyperbilirubinaemia, chronic active hepatitis, alcoholic hepatitis and Gilbert's syndrome (disease).

The *post-hepatitic syndrome* and chronic benign hepatitis may be identical in their subjective manifestations. The function of the liver in the post-hepatitic syndrome remains normal, whereas chronic hepatitis is marked by a more or less obvious continuous or periodic hyperbilirubinaemia and an almost constant increase in transaminase activity.

Post-hepatitic hyperbilirubinaemia is also characterized by the absence of a concomitant increase in transaminase activity. The final diagnosis of this syndrome may be established only from the results of liver biopsy which should be performed no earlier than the terms indicated above. To obtain comparative results the biopsy is repeated, but usually no earlier than in six months.

Chronic active hepatitis differs from the benign form first and foremost by such signs as hepatomegaly, spider naevi and splenomegaly. The serum globulin content is increased in active hepatitis but normal in benign hepatitis. Morphological examination reveals disorders of the hepatic lobular structure and other signs in active hepatitis. In some cases, signs of active hepatitis are found in one portal zone and signs of benign hepatitis in another. The final diagnosis in such cases may only be made from the results of long-

term follow-up of the disease and from the results of repeated liver biopsy.

Enlargement of the liver due to its *fatty infiltration* is a frequent occurrence in alcoholism. Although such a liver is often tender to palpation it usually functions normally. Information on the abuse of alcohol and other signs of alcoholism allow alcohol-induced fatty infiltration of the liver to be differentiated from chronic benign hepatitis. The final diagnosis is based on the results of needle biopsy.

In appraising the results of biopsy, it is necessary to bear in mind that after a more or less lengthy period of abstinence from alcohol, the signs of alcoholic affection of the liver (fatty degeneration of hepatocytes, alcoholic hyaline, focal necroses of the liver cells with concomitant polymorphic cellular infiltration) may completely disappear as the result of which the histological picture of the specimen cannot be distinguished from that in chronic benign hepatitis.

Gilbert's syndrome (*disease*) is often misdiagnosed as chronic hepatitis. As in a case of benign chronic hepatitis, the syndrome is often discovered by accident during examination of the patient for some other disease. In these patients hyperbilirubinaemia is caused by the accumulation of indirect bilirubin fraction in blood and it is therefore never attended by bilirubinuria.

Blood transaminase activity is normal and the rate of bromsulphalein and Bengal rose excretion does not change.

According to the findings of needle biopsy, the structure of the liver is normal, but histochemical examination often reveals a reduced content in the hepatic cells of uridine-diphosphate-glucuronyl-transferase, an enzyme which catalyses the reaction of bilirubin conjugation with glucuronic acid.

Chronic active (aggressive) hepatitis. The classical type of active hepatitis is often called lupoid hepatitis. Other types of this syndrome are encountered in patients with a history of acute virus B hepatitis and alcoholic hepatitis. Active hepatitis is also observed in congenital diseases of the liver, namely, hepatolenticular degeneration and alpha-1-antipepsin deficiency, and after long-term medication with purgatives and hypotensive agents.

Lupoid hepatitis begins insidiously in approximately two thirds of patients and acutely in one third of cases. The disease is prevalent among young women. At first it is mistaken for ordinary acute hepatitis, and only unsuccessful therapy obliges the physician to reconsider the diagnosis and recognize a chronic disease. Despite treatment, the disease advances. The liver and spleen are considerably enlarged. Enlargement of the left hepatic lobe is particularly characteristic and it is often mistaken for the spleen in such cases.

In typical cases, jaundice develops during exacerbation of the

disease and a great number of spider naevi appear. During a remission the blood bilirubin content becomes normal and the number of spider naevi reduces sharply. The clinical picture of cirrhosis develops in the late stages of the disease. The liver grows smaller and ascites, oedema and encephalopathy develop. Although there are occasional reports on the possibility of complete recovery, lupoid hepatitis terminates in cirrhosis as a rule today.

Besides the liver, many other organs and systems are always affected in active lupoid-type hepatitis. Affection of the kidneys is usually manifested by glomerulonephritis with more or less pronounced proteinuria. Lupus cells are found in the blood of some patients suffering from fever of long standing. Hyperplasia of the reticuloendothelial system is sometimes displayed by generalized lymphadenopathy. Affection of the endocrine organs leads to the development of acne, hirsutism, skin striae, amenorrhoea, gynaecomastia and a cushingoid face. Haemolytic anaemia with leucopenia and thrombocytopenia is sometimes discovered in these patients. Pronounced auto-immune disorders approximate lupoid hepatitis with systemic lupus erythematosus.

It is very difficult to make the differential diagnosis between these diseases. As pointed out by Nasonova (1972), the final diagnosis should be based on the features of the clinical couse of the disease. An early diagnosis of lupoid hepatitis is naturally very rare.

Chronic active hepatitis usually develops after acute hepatitis caused by B virus and other viruses with the exception of A virus. Usually this acute hepatitis takes a chronic course in individuals with altered humoral immunity. The developing clinical picture is a mitigated variant of lupoid hepatitis. The disease occurs more frequently among males than among females. Most of the patients are over 30 years of age. In about 50 per cent of cases chronic active hepatitis proves to be a continuation of the acute form, whereas in the other 50 per cent the onset is unnoticed.

Chronic active hepatitis may be asymptomatic for some time. The diagnosis in such cases is based on the clinical findings (enlargement of the liver and often of the spleen), the results of biochemical tests (long-term, at times undulating increase in transaminase activity) and the results of biopsy.

The disease is marked far more frequently by the development of jaundice from time to time, more or less protracted periods of subfebrile temperature, arthralgia and hyperfermentaemia. The multisyndrome character typical of lupoid hepatitis is very moderate. A slowly progressive disease terminates in the development of cirrhosis or primary carcinoma of the liver.

Hepatitis induced by B virus is sometimes disclosed by chance and at times after the patient had applied to the doctor because

of jaundice, the dyspeptic syndrome or unpleasant sensations in the right hypochondrium. The moment when the disease had begun remains a mystery. We may speak of *chronic hepatitis* only in those instances when an enlarged firm liver, a large spleen, and dysproteinaemia are found. In all other cases the physician has to decide whether the patient is suffering from acute hepatitis or exacerbation of chronic hepatitis.

Full recovery from acute viral hepatitis is possible. The diagnosis of *acute viral hepatitis* may be ruled out only after a lengthy follow-up period. If the dimensions of the liver, the bilirubinaemia level and transaminase activity are normalized, acute hepatitis may be presumed. The final diagnosis may only be made from the results of biopsy which should be performed six or twelve months after the clinical manifestations of the disease have disappeared.

It is even more difficult to rule out *chronic benign (persistent) hepatitis.* In discussing the differential diagnosis of such cases it is necessary to focus special attention at the different degrees of manifestation of one and the same signs. An enlarged spleen, high transaminase activity and high bilirubinaemia are more typical of active than of persistent hepatitis. The final diagnosis may only be made from the results of repeated biopsies.

Pericholangitis often develops in attendance to non-specific ulcerative colitis and Crohn's disease. Like chronic active hepatitis, it is also complicated by cholestasis in rare cases. In discussing the diagnosis in such cases, particular significance should be attached to the degree of the following signs. The contents of globulins and antibodies to mitochondria in blood are increased in chronic active hepatitis, but normal in pericholangitis. The alkaline-phosphatase level is elevated in pericholangitis, but normal in chronic hepatitis. The final diagnosis is based on the findings of needle biopsy.

Hepatolenticular degeneration is sometimes manifested for the first time by moderate hepatomegaly combined with short-term jaundice, dysproteinaemia, thrombocytopenia and signs of portal hypertension. In the clinical picture, Konovalov-Wilson's disease may be no different at certain stages from chronic active hepatitis. Hepatolenticular degeneration is a hereditary disease usually manifested in childhood. A brown ring around the iris (Kayser-Fleischer ring) is a pathognomonic sign of hepatolenticular degeneration. It is easily detected on examination of the patient with a slit lamp. The advancement of hepatolenticular degeneration may be successfully arrested if diagnosed in good time. It is recommended to examine without fail every patient under thirty suffering from chronic hepatitis in collaboration with an ophthalmologist using a slit lamp for early recognition of the disease. Increased content of copper and ceruloplasmin in blood and increased excretion of copper in the urine confirm the diagnosis.

Chronic active hepatitis may be induced by drugs (*drug-induced hepatitis*). Particularly notorious in this respect are Tegretol used in the treatment of neuralgia of the trigeminal nerve, Aldomet (Dopegit) used widely as a hypotensive agent, and immunodepressants. It was recently disclosed that prolonged use of isophenine, a commonly used purgative, also leads to the development of chronic active hepatitis.

The clinical and biochemical signs of drug-induced hepatitis usually disappear soon after medication with the agent causing it is discontinued. The cause of drug hepatitis is obviously hypersensitization of the body because persistent medication with these agents, despite hepatomegaly, hyperbilirubinaemia and hyperfermentaemia, results in the development of lupoid-type hepatitis with involvement of the joints, and the appearance of high titres of antibodies to different ingredients of the nucleus and of lupus erythematosus cells in blood.

Cirrhosis of the Liver

In 1974 the international association for study of the liver suggested distinguishing cirrhoses according to their aetiology and morphology. Cirrhoses of the liver with which the internist has to deal most frequently in discussing problems of differential diagnosis may be grouped (Supplement XVI-1) into congenital and acquired. Cirrhosis developing after viral hepatitis and alcohol-induced cirrhosis are particularly common in the latter group. Other forms of infectious cirrhosis (syphilitic, tuberculous, actinomycotic) are extremely rare, because involvement of the liver in these diseases is diagnosed in the stage of hepatitis.

Infectious cirrhosis. This term designates cirrhosis which is the terminal stage of the evolution of virus forms of hepatitis. The clinical picture of cirrhosis is the same in all cases. It depends neither on the aetiology nor on its morphology. If cirrhosis develops in a patient with active hepatitis, the signs of the hepatitis add certain features to the typical picture of 'pure' cirrhosis.

Contemporary knowledge on the association of cirrhosis with hepatitis is mainly based on the results of long-term follow-up of infection with B hepatitis virus which is easily identified. Depending on the extent of the necroses developing in the acute period in a patient who had suffered from hepatitis induced by B virus, micronodular, macronodular, mixed or multinodular (incomplete septal) type of cirrhosis may develop.

The possibility of necrosis developing after infection with A hepatitis virus is considered hardly possible to date. The associa-

tion of cirrhosis with hepatitis induced by other viruses has not been studied.

The diagnosis of far advanced cirrhosis in patients with a characteristic appearance presents no difficulties and may be established without resorting to special methods of examination. In less manifest cases cirrhosis may be suspected if the patient has an enlarged liver and a history of jaundice or there is evidence of long abuse of alcohol.

Hepatomegaly is the most common sign of cirrhosis and is found in 67 per cent of cases of this disease. In one third of cases the liver is normal in size or even smaller than usual. Its border is usually sharp, painless and firm. The non-uniform enlargement of the liver is a characteristic feature. Its right lobe may be smaller than normal, while the left is enlarged. Unfortunately, this easily detected sign is rare. The probability of cirrhosis gains firmer ground when, together with hepatomegaly, signs of portal hypertension (ascites, dilated veins of the mucous membrane of the lower third of the oesophagus and the cardia, splenomegaly and jaundice) are detected. Ascites is found in 60 per cent whereas jaundice and dilatation of the oesophageal veins in only 50 per cent and splenomegaly in 40 per cent of cases with cirrhosis. Spider naevi acquire diagnostic significance only when they are found en masse.

The objective signs of cirrhosis listed above are usually combined with complaints of fatiguability, weakness, anorexia and abdominal discomfort. Hepatic functions are impaired in most cases. The secretory function suffers earlier and most severely. Characteristic features are hypoalbuminaemia and hypoprothrombinaemia; the rate of albumin and prothrombin synthesis and disintegration is drastically reduced in cirrhosis. An increased content of immunoglobulins is demonstrated on the electrophoregram by the characteristic increase in globulins whose peak concentration occurs in the middle, between the beta- and gamma-fractions.

The listed symptoms are far from always encountered in each case of cirrhosis. Patients are often unaware that they are ill, and the disease is a chance finding on autopsy. According to relatively recent statistics (1970) the incidence of such cases is 19 per cent. Cases of asymptomatic cirrhosis are particularly common among the elderly.

All the clinical signs of cirrhosis discussed are not specific. A similar clinical picture is encountered in some diseases of the cardiovascular system. The diagnosis of cirrhosis must therefore always be founded on unquestionable signs, namely, the general appearance and the microscopic structure of the liver. The character of the surface of the liver and its colour, the size of the spleen and, in many cases, also the pronounced collateral circulation may be appraised during laparoscopy which it is recommended to supplement by

biopsy of several hepatic areas in all cases. Microscopy of the preparations allows the morphology of the cirrhosis and the activity of hepatitis and the cirrhotic process to be appraised.

The activity of hepatitis is judged by the presence of necrotic foci and attendant inflammatory reaction, and the activity of cirrhosis by the tinctorial properties of the connective tissue basic substance, the appearance of the fibroblasts, and the degree of maturity of the connective tissue fibres.

An enlarged and tender liver in combination with ascites and dyspnoea on movement is a constant finding both in cirrhosis and in *right-ventricular failure*. It is relatively easy to differentiate these syndromes if the order in which various complications develop can be traced and the mechanism of their development determined.

In heart failure disorders of water-electrolyte metabolism are first displayed as oedema of the subcutaneous tissue of the shins and feet. By the time ascites develops, the patient is incapacitated and often cannot even move unassisted in the room. In cirrhosis, ascites develops before anasarca. Despite the large ascites and complaints of dyspnoea, patients with cirrhosis move about easily and are even capable of looking after themselves. This is explained by the fact that ascites in these patients is mainly caused by local factors while dyspnoea is caused by a high position of the diaphragm.

An enlarged spleen is found only in far advanced cases of right-ventricular failure with signs of tricuspid insufficiency and often with disorders of the heart beat rhythm. Splenomegaly may even be encountered in the initial stages of cirrhosis. Right-ventricular failure is easily distinguished from cirrhosis by scanning of the liver. Cirrhosis is characterized by reduced uptake of the radioactive medium by the liver and its increased uptake by the spleen.

It should also be taken into account that hepatomegaly, elevated venous pressure, and other signs of right-ventricular failure in heart diseases develop in attendance to signs of left-ventricular failure which had appeared earlier. The size and shape of the patient's heart are abnormal, as a rule. The increased blood filling of the lungs usually persists after right-ventricular failure develops. In cirrhosis there are usually no signs of increased pulmonary blood filling. The size and shape of the heart are normal and there is a sinus rhythm.

The medical history and signs attendant to cirrhosis or a heart disease complicated by circulatory failure of the right-ventricular type help greatly in the differential diagnosis of these two syndromes. The differential diagnosis is made with confidence at the patient's bedside if all the data listed above are taken into account.

Alcoholic cirrhosis. The abuse of alcohol leads to the accumulation of fat in the hepatocytes. Fatty degeneration of the liver is

usually accompanied by mild inflammation with the formation of 'fat granulomas'. In severer cases alcoholic hepatitis develops with a morphological picture resembling that of active chronic hepatitis. Alcoholic hyaline deposits in the hepatocytic protoplasm are a characteristic sign. Areas of hyaline necrosis in alcoholic hepatitis are arranged around the central veins. Cicatrization of the necrotic areas is attended by compression of the veins and the development of portal hypertension. Inflammatory infiltrates of mononuclear cells appear in the interlobular septa. Proliferation of the biliary capillaries develops in attendance. The picture of micronodular (Laennec's) cirrhosis of the liver develops. The coexistence of signs of cirrhosis with signs of hepatitis and fatty degeneration of the liver is considered to be characteristic.

Alcoholic cirrhosis develops only after years of alcohol abuse. The disease occurs most frequently in males with an average age of 50 years. The initial stages of cirrhosis are often unnoticed by the patient. They are manifested by non-specific symptoms such as weakness, anorexia and abdominal pain. Examination usually reveals atrophy of the testes, female-type pilosis in males and signs of alcoholic polyneuritis with typical atrophy of the thigh muscles. The liver is enlarged in the early stages of cirrhosis, but grows smaller in the late stages. Splenomegaly is found in about one third of patients.

Alcoholic hepatitis is sometimes complicated by cholestasis and is often misdiagnosed as infectious hepatitis. Alcoholic cirrhosis, in precisely the same manner, may be mistaken for cirrhosis consequent upon virus hepatitis. If the following circumstances are weighed the differential diagnosis of these types of cirrhosis may be arrived at sooner. Cholestasis causes no pain in infectious and drug-induced hepatitis as a rule, while in alcoholic hepatitis and cirrhosis it is often marked by abdominal pain and is never total. The pain is usually felt around the umbilicus and in the epigastrium. It is commonly attributed to concomitant alcoholic pancreatitis.

Alcoholic hepatitis and cirrhosis are always attended only by moderate increase in transaminase activity, though bilirubinaemia may be very high. This is explained by a sharper affection of the secretory hepatic function. The final diagnosis of alcoholic cirrhosis is established from the findings of morphological examination of the liver: the simultaneous existence of signs of fatty degeneration of the hepatocytes, alcoholic hyaline and micronodular cirrhosis.

Biliary cirrhosis of the liver, whether primary or secondary, is always marked by jaundice. Although hepatomegaly is its constant sign, jaundice always predominates in the clinical picture. This is why the disease has to be differentiated from jaundice of other origin and not from cirrhosis of the liver. The differential diagnosis of

primary biliary cirrhosis of the liver is discussed in the chapter 'Jaundice'.

Congenital cirrhoses of the liver. *Haemochromatosis.* The term haemochromatosis is used to designate two diseases: hereditary (primary) haemochromatosis characterized by the accumulation of large amounts of iron in the internal organs, and acquired (secondary) haemochromatosis which is sometimes encountered in chronic anaemias and in excess of iron in the body brought in with the food, beverages and drugs. The disease is marked by disorders of haemosiderin, haemofuscin and melanin metabolism. The liver, pancreas, bones, kidneys, gastro-intestinal tract, endocrine glands, bone marrow, skin, and heart are mainly involved.

The morphological and clinical signs of secondary haemochromatosis in chronic anaemias occur under the effect of blood transfusions repeated many times or prolonged medication with oral iron preparations. Haemochromatosis in sideroblastic anaemias (see chapter 'Anaemias') usually appears before blood transfusion therapy is begun. Haemosiderosis in such cases is attributed to increased iron absorption in the gastro-intestinal tract.

Some authors link the increased content of iron in the liver of patients suffering from cirrhosis with the commonly attendant anaemia, others associate it with the high content of iron in water used for the preparation of alcoholic beverages habitually taken by most of these patients. Secondary haemochromatosis encountered in certain African tribes is explained by the high content of iron in food cooked in iron utensils. Haemochromatosis always develops in patients with portacaval anastomosis created in the management of cirrhosis of the liver.

Primary haemochromatosis remains asymptomatic for a long time. Pigmentation of the skin, diabetes mellitus, hepatomegaly, cardiomyopathy, and arthropathy appear in most cases between the ages of 45 and 55. Signs of secondary haemochromatosis usually appear at a younger age. The incidence of the disease among males is about tenfold that among females. The rare occurrence of the disease among females is explained by the regular loss of iron during menstruation.

Haemochromatosis is a disease of many syndromes. More or less severe involvement of all internal organs is encountered in far advanced cases of the disease. Affection of the liver, skin, pancreas, heart, and joints occurs most often and is more severe. Modern therapeutic methods prolong the patient's life considerably, but nonetheless fail to arrest the development of the disease completely. Death occurs from an attendant infection, hepatic coma or heart failure.

Hepatomegaly is the most common sign of haemochromatosis and is encountered in more than 90 per cent of cases. The liver is

characteristically firm. Its surface is smooth and its border sharp and painless. The left lobe is often much larger than the right. An enlarged spleen with a firm rounded border is palpated in about two thirds of patients. Ascites in haemochromatosis may be a consequence of portal hypertension or of heart failure. Other signs of portal hypertension (varicosity of the subcutaneous veins, bleeding from the oesophageal veins) are rare.

Increased pigmentation of the skin with melanin is found in approximately 90 per cent of cases. The skin may be bronzed (which was reflected in the obsolete designation of the disease 'bronzed diabetes'), bluish black or slate coloured. Pigmentation is most conspicuous on the face, neck, forearms, dorsal surfaces of the hands, perineum, genitals, umbilicus, old scars, and nipples. In about 20 per cent of cases the oral mucosa and conjunctiva are pigmented.

Diabetes mellitus is considered to be the third classical sign of haemochromatosis. It is encountered in 75 per cent of cases, i.e. somewhat less frequently than melanoderma and hepatomegaly. In about 30 per cent of patients, diabetes mellitus precedes the other signs of the disease by several years. It usually takes a severe course from the very onset and becomes insulin-resistant. All the complications of diabetes (retinopathy, glomerulosclerosis, pyelonephritis, polyneuritis) develop with time.

Haemosiderin deposits in the heart are first localized under the ventricular epicardium. Diffuse myocardial fibrosis with deposits of haemosiderin in the muscle fibre develops later. Involvement of the heart (restrictive cardiomyopathy) is encountered in about half the cases of haemochromatosis and is manifested by disorders of cardiac rhythm and heart failure. Progressive heart failure may cause the patient's death.

Acute synovitis of the small articulations of the hands occurs in almost 50 per cent of cases of haemochromatosis. Progressive polyarthritis is encountered in rare cases. With the development of the disease the secondary sex characteristics regress. Amenorrhoea develops in females; loss of facial, pubic and axillary hairs occurs in males. The testes grows smaller gradually.

The diagnosis of haemochromatosis is easily made in the late stages of the disease when all three classical signs (hepatomegaly, skin pigmentation, and diabetes mellitus) have already developed. The discovery of the clinical signs of cardiomyopathy, arthropathy, and hypogonadism leaves no room for doubt. This combination of signs, however, appears only in the late stages of the disease.

The diagnosis may be made earlier if needle biopsy of the liver is performed more frequently. Biopsy of the liver or laparoscopy with biopsy is considered indicated in all cases of diabetes mellitus attended by hepatomegaly and in insulin-resistant diabetes. Increased content of iron in the hepatocytes (parenchymatous siderosis)

and in the reticuloendothelial cells (reticuloendothelial siderosis) is the most reliable diagnostic sign of haemochromatosis.

If biopsy of the liver cannot be undertaken for some reason, the differential diagnosis between primary haemochromatosis and the secondary form may be made by examining the sternal punctate or peripheral blood leucocytes. In haemochromatosis the haemosiderin particles in the leucocytes are small and of a regular round shape. In secondary haemochromatosis the haemosiderin particles are much larger.

High differential diagnostic significance is attached to the clinical findings. Anaemia is an almost obligatory sign of secondary haemochromatosis. In contrast, it is absent at the onset of primary haemochromatosis and is very moderate in the later stages when cirrhosis of the liver develops.

Diabetic coma was the most common complication of haemochromatosis in the past. The survival of patients is considerably greater today, and restrictive cardiomyopathy with disturbed heart rhythm and heart failure, hepatic coma, tumours of the liver, and particularly cholangiocarcinoma and sarcoma are currently the most frequent complications of the disease.

Hepatolenticular degeneration. Konovalov-Wilson's disease, or hepatolenticular degeneration, is a rare disease. It is transmitted as an autosomal recessive character. The clinical manifestations of the disease are caused by disorders of copper metabolism. Copper is stored in excessive amounts in the liver, kidneys, cornea and brain (in its dentate, lentiform and caudate nuclei, globus pallidus, cerebellum and other parts). The positive copper balance may be converted to a negative balance by means of modern methods of treatment, thus changing the prognosis of the disease. Timely diagnosis not only saves the patient's life but preserves his working capacity for a considerable length of time.

In 50 per cent of cases the disease sets in in childhood and adolescence with affection of the liver manifested by hepatomegaly, a feeling of heaviness and pain in the right hypochondrium, and more or less pronounced jaundice. Much less often the disease begins with haemolytic anaemia which may be moderate but becomes severe sometimes because of recurrent crises. Most patients come to the physician with hepatomegaly, anaemia, and jaundice of mixed hepato-cellular and haemolytic origin.

Long-term follow-up of patients and repeated examination showed that the deposition of copper is attended by an inflammatory reaction. It is presumed that the events develop in the following order. Fatty dystrophy occurs first in the hepatic cells and is later joined by inflammation in the region of the portal tract. The result of this process is the development of micronodular cirrhosis with portal hypertension. In the clinical course the disease resembles undulant

chronic active hepatitis. The younger the patient, the more fulminant the disease. It is distinguished from aggressive hepatitis only by the presence of extrapyramidal disorders, obvious impairment of the intellect, and affection of the kidneys manifested by haematuria and aminoaciduria. In some cases, adult-type complete Fanconi's syndrome develops.

In adolescence, the disease usually begins with extrapyramidal disorders. Sharp increase of involuntary twitching at a moment when extreme precision of movement is required is a characteristic feature. This is soon joined by hepatomegaly, splenomegaly, ascites, and varicosity of the oesophageal veins. Affection of the kidneys is found in every case of this form which is also 'lenticular' and usually more benign than the 'hepatic' form described above. Sooner or later the disease is complicated by copper-containing pigment deposits on the corneal periphery.

The Kayser-Fleischer ring may sometimes be seen with the naked eye, but when it is not fully manifested examination of the patient with a slit lamp is advisable. The detection of this sign is equivalent to establishing the diagnosis of hepatolenticular degeneration, because this sign is never encountered in any other disease.

One must never rule out the possibility of hepatolenticular degeneration in any case when a child or adolescent has an enlarged liver of unknown aetiology. Presumption that the patient has Konovalov-Wilson's disease becomes ever more substantiated if signs of increased haemolysis (jaundice, increased number of reticulocytes in blood) are found.

The diagnosis is verified by the disclosure of increased excretion of copper in the urine and a low content of copper and ceruloplasmin in blood. A temporary decrease in blood ceruloplasmin concentration occurs in any severe hepatitis. With the improvement in the patient's general condition, it returns to normal level. A low blood ceruloplasmin content is a constant sign of Konovalov-Wilson's disease.

Alpha-1-antitrypsin deficiency. The synthesis of alpha-1-antitrypsin is regulated by at least 13 autosomal genes. Nine different alleles of these genes have been identified to date. The accumulation of alpha-1-antitrypsin in the hepatocytes leads to the development of micronodular cirrhosis the advancement of which is sometimes complicated by cholestatic-type jaundice. The development of cirrhosis is attributed to the direct toxic effect of antitrypsin on the hepatocyte or to increased copper content in the hepatocyte.

According to the findings of autopsy, cirrhosis of the liver occurs in approximately 40 per cent of persons homozygous in any of the 17 protease inhibitor phenotypes identified to date. Congenital alpha-1-antitrypsin deficiency is always complicated in an adult also by obturation pulmonary emphysema, the progress of which can be arrested by abstinence from smoking.

The possibility of cirrhosis being associated with alpha-1-antitrypsin deficiency should be assumed in every patient with signs of simultaneous affection of the liver and lungs. For revealing congenital alpha-1-antitrypsin deficiency it is recommended to perform biopsy and treat the hepatic sections by special methods in every case of cirrhosis of uncertain origin. If characteristic glycoprotein-containing inclusions are detected in the hepatocytes, the patient must be subjected to genetic examination. The final diagnosis of cirrhosis induced by alpha-1-antitrypsin deficiency may only be established after the patient's phenotype is determined, according to protease inhibitors.

Cirrhosis sometimes develops in other hereditary diseases. It is a particularly constant occurrence in thalassaemia and other haemolytic anaemias. Affection of the liver in this group of diseases is explained by the development of secondary haemochromatosis.

Cirrhosis of the liver is a component of the clinical picture of hereditary metabolic diseases, most of which develop in childhood. Patients with mucoviscidosis, congenital telangiectasias, histiocytosis X, galactosaemia and congenital fructose intolerance sometimes reach adolescence and middle age. The medical history and manifestation of the hereditary diseases mentioned help in identifying the causes of cirrhosis in these patients.

Gaucher's disease. Hepatomegaly and splenomegaly are among the constant signs of some congenital disorders of lipid metabolism. Gaucher's disease is the most commonly encountered. Only the chronic form of this disease is encountered in adults.

In most cases the disease begins with pains in the bones of the lower limbs. They are so intensive that are sometimes misdiagnosed as acute osteomyelitis. The pains are linked with bone marrow infiltration by Gaucher's cells. The destructive changes are most pronounced in the vertebrae and femur. Marked deformity of the distal femur is a particularly characteristic feature.

Hepatomegaly and splenomegaly are very moderate in some cases and considerable in others. Infiltration of the liver by Gaucher's cells is attended by impairment of its normal lobular structure. Proliferation of interlobular connective tissue leads to the development of portal hypertension with ascites and hyperbilirubinaemia. Disturbances of other hepatic functions do not attend every case.

Focal skin pigmentation and changes in the conjunctiva are the most characteristic external signs of the disease. The focal skin pigmentation resembles chloasma of pregnancy. It is distinguished from chloasma in that its intensity does not depend on solar radiation. Wedge-like brown thickenings of the conjunctiva form on both sides of the pupils. This pathognomonic sign of Gaucher's disease may only be detected in bright daylight.

Far advanced cases of Gaucher's disease are marked by anaemia, leucopenia and thrombocytopenia, petechiae and ecchymoses on

the skin and mucous membranes, and haemorrhages into the serous cavities. The final diagnosis is made from the results of liver or bone-marrow biopsy.

Cysts and Tumours of the Liver

Cysts and tumours are rare diseases of the liver. We set them apart in a separate group because they are manifested by isolated enlargement of the organ as a rule. Simultaneous enlargement of the spleen is extremely rare. We give preference to the aetiological classifications of these structures because they meet the requirements of differential diagnosis far better than any other classifications.

Cysts of the liver. Congenital and acquired, parasitic and non-parasitic cysts are distinguished.

Non-parasitic congenital cysts of the liver are a consequence of disorders in the processes of degeneration of intrahepatic bile ducts. They may be solitary or multiple. *Acquired cysts* are of traumatic origin. They sometimes occur several weeks or months after severe injury to the hepatic region.

The incidence of congenital cysts of the liver among females is four- to fivefold that among males. Both solitary and multiple cysts may produce no symptoms for a lengthy period of time. Growing slowly, they begin exerting pressure on the adjoining organs. This gives rise to many symptoms and signs among which hepatomegaly, abdominal pain, and disturbed function of the adjacent organs are very common. Polycystic liver disease is often combined with polycystic kidney disease. In most cases, the clinical signs of the disease appear for the first time between the ages of 30 and 50.

The patients usually visit the doctor because of heaviness in the right hypochondrium, enlarged abdomen or abdominal pain. Abdominal palpation reveals moderate or considerable enlargement of the whole liver or of only one of its lobes. A rounded mass with an even surface is sometimes felt in the abdominal cavity. In a case in our practice the patient herself found this tumour, and it was only afterwards that she complained of abdominal distension and attacks of abdominal pain after a meal which were attended by nausea and sometimes by vomiting.

The attacks of abdominal pain may be caused by haemorrhages into the cavity of the cyst, rupture of small cysts or rupture of a cyst into adjoining organs. Compression of the neighbouring biliary duct may lead to jaundice, while infection of the cyst to an abscess of the liver.

A tentative diagnosis of a hepatic cyst may be made in every case of hepatomegaly when there are neither disorders in the function of the organ nor complaints. The diagnosis becomes more probable if it is found that the patient is suffering from hepatomegaly for many years and also has signs of polycystic kidney disease. The final diagnosis may be established only after parasitic cysts of the liver and other tumours of the upper abdomen have been ruled out.

Ecchinococcosis of the liver. Two types of human hydatid disease of the liver are distinguished, alveolar and cystic. The routes of infection in both diseases are the same. Cystic ecchinococci may be unilocular (accounting for 75 per cent of all cases) or multilocular. Most unilocular ecchinococci (approximately 80 per cent) are found in the right hepatic lobe on its anterior or inferior surface. Much less frequently the hydatid cystis located on the superior or posteroinferior surface of the liver. The growth of cysts of this localization is attended by considerable displacement of the diaphragm. The cysts grow very slowly and are asymptomatic for many years.

The disease is often discovered by chance during X-ray examination. Drastic upward bulging of the right diaphragmatic dome is particularly suggestive of the disease. A cyst growing downward from the inferior surface of the left hepatic lobe resembles the spleen but may nevertheless be differentiated from it by the character of movement during respiration. The liver with the hydatid cyst moves downward, whereas the spleen moves from left to right and downward at an angle of about 45 degrees. A cyst lying on the anterior or inferior surface of the liver has an elastic consistency and is painless. The surface of an unilocular ecchinococcus is always smooth while the surface of a multilocular cyst is always lobular.

Pains occur in 50 to 80 per cent of cases with hydatid disease of the liver. Their localization is determined by the size of the cyst and its localization on the surface of the liver, and the presence of adhesions with the peritoneum, diaphragm and other organs adjoining the cyst. A cyst close to the hepatic porta compresses the portal vein with its gradual growth and may lead to ascites. Jaundice develops when the growing cyst compresses the large biliary ducts. According to Akhrem-Akhremovich (1965), these complications are encountered in 5-6 per cent of cases of hydatid disease of the liver.

The hydatid cysts may sometimes rupture either spontaneously or as the result of injuries. Rupture of the cyst is marked by a clinical picture of anaphylactic shock, as a rule. Rare cases of asymptomatic rupture of a cyst are encountered.

A tentative diagnosis of hepatic hydatid cyst may be made when a tumour of the liver is found in individuals living in regions where this disease is widespread or in individuals who had lived in such places. Increased blood eosinophil count is found in more than half the patients. X-ray methods of examination are always used for

revealing hydatid cysts of the liver. Calcification of the cyst is sometimes demonstrated on the radiograph. The presence of foci of calcification distinguishes hydatid cysts from congenital cysts. A congenital cyst never calcifies.

Isotope and ultrasonic scanning of the liver may yield indirect confirmation of the diagnosis. Cysts growing on the anterior and inferior surfaces of the liver may be examined by laparoscopy. When viewed through a laparoscope, a hydatid cyst is white and has a rounded border. In distinction from congenital cysts and malignant tumours, it is always surrounded by adhesions and a corona of dilated vessels.

Immunological methods of diagnosis are more specific and more sensitive. Casoni's intracutaneous test is positive in 75 per cent of cases. False positive results are produced in 18 per cent of cases. The haemagglutination reaction is more specific and yields positive results in up to 83 per cent of cases. The strictly specific immunophoresis test, in which fluid from the hydatid cyst is used as the antigen, produces positive results in 85 per cent of cases. This test is negative in cases of an inactive parasitic cyst caused, for instance, by complete calcification of its capsule.

The alveolar ecchinococcus always develops primarily in the liver. In the larval stage the causative agent forms small cysts with a jelly-like content. There is no surrounding capsule and numerous daughter cysts form continuously on its periphery. Necroses often develop in the infiltratively growing tumour and their resolution leads to the formation of cavities filled with a fluid. The tumour may metastasize by the haematogenic or lymphogenic route.

The invasion remains asymtomatic for a lengthy period and is manifested for the first time by a feeling of heaviness in the epigastrium and right hypochondrium. Pain is usually mild.

'Extraordinary firmness' of the liver is a characteristic sign of alveolar ecchinococcosis (Akhrem-Akhremovich, 1965). The spleen is enlarged in about one third to one half of the cases. Disintegration of the tumour is attended by fever and leucocytosis. In the later stages of the disease, all patients have an enlarged liver and total or partial obstruction of the bile ducts and resulting jaundice. Eosinophilia is found in many cases. The disease is thought to be a malignant tumour of the liver until specific diagnostic tests are carried out.

Tumours of the liver. Countries and continents differ considerably in the incidence of tumours of the liver, but in all countries carcinoma is the most frequently encountered tumour of this organ. In recent times, tumours of the liver have been encountered far more frequently in Europe than ever before. This is rather to be explained by the older age of its population. Carcinoma of the liver usually occurs in persons over 60 years of age. According to histological

structure, the following primary tumours of the liver are distinguished: hepatoma (tumour growing from the hepatocytes), cholangioma (tumour growing from the epithelium of the biliary ducts), sarcoma (tumour growing from the interlobular connective tissue), haemangioendothelioma (haemangiosarcoma, sarcoma arising from the Kupffer cells), and mesenchymoma (a mixed tumour).

The blood of all abdominal organs passes through the liver, and not only primary tumours but metastases of tumours growing primarily in other organs are therefore found in it. In regard to carcinoma it has been established that the incidence of its metastases in the liver is twentyfold that of primary tumours (Bloomenthal and Spellberg, 1971). Moreover, metastases are found in the liver in 30-50 per cent of all persons who had died from carcinoma.

A benign tumour of the liver is a rare disease. The numerous variants of the structure of benign tumours provide the grounds for distinguishing teratomas and epithelial and mesenchymal tumours. Haemangiomas and adenomas arising from the epithelial cells of the liver (hepatocellular adenoma) and bile passages (cholangioadenoma) are rather more common than other tumours. They have been encountered much more frequently in the past ten years than previously. Many authors attribute this to the wide use of hormonal contraceptives (O'Sullivan and Wilding, 1974).

Primary carcinoma of the liver. Hepatomegaly is found in most cases of primary carcinoma of the liver. The right lobe of the liver is most frequently enlarged when the tumour grows from one centre. Multicentral growth of the tumour is marked by irregular, usually moderate enlargement of the organ, with the left lobe sometimes larger than the right. Diffuse uniform enlargement of the liver is rare and in all our cases it was attended by enlargement of the spleen.

In 2 to 20 per cent of cases the tumour grows asymptomatically, but in most patients enlargement of the liver is attended by a feeling of extraordinary fullness and distension in the epigastrium to which dull pain soon appears in attendance. The pain is usually localized on the right side, right hypochondrium or epigastrium. Tareev and Afanasyeva (1965) attribute these pains to stretching of the Glisson capsule or to concomitant perihepatitis. Sharp, distinctly localized pains in the ribs or vertebrae usually appear in the late stages of the disease and are explained by metastases of the neoplasm.

It was long considered that remote metastatic spread of primary carcinoma of the liver is very rare. It has now been established that symptoms and signs caused by metastases in the ribs, vertebrae or spinal cord are in 1.5 to 5.3 per cent of cases the earliest clinical manifestations of primary carcinoma of the liver. In later stages metastatic spread to the lungs occurs in 8.3 per cent of patients. In making the differential diagnosis it is particularly important to bear in mind that metastatic spread of hepatoma to the lymph

nodes of the hepatic porta is encountered only in 3.4 per cent of cases. Much more frequently the tumour grows into the adjacent organs (diaphragm, stomach, duodenum, adrenals).

Hepatoma, whether diffuse or growing from one node, is marked by rapid and considerable enlargement of the liver in all directions. Hepatomegaly is found in more than 90.7 to 92 per cent of cases of these types of the disease. The lower border of the liver is always of a stony consistency, non-tender and reaches down to the level of the umbilicus. Its superior boundary rises to the fourth rib in half of the cases. Enlargement of the anteroposterior chest dimensions is simultaneously found. In about 50 to 75 per cent of cases the growth of the tumour is attended by moderate fever. High fever with chills is rare. Antibiotics have no effect on the fever because its development, like the development of leucocytosis, is associated with the resolution of necroses and extravasations regularly occurring in the growing tumour.

As it grows, the tumour gradually compresses the adjacent organs or grows into them. A consequence of this is portal hypertension with gradually developing ascites, splenomegaly and sometimes dilatation of the oesophageal veins. Portal hypertension is not the only cause of ascites. One easily becomes convinced of this at autopsy: ascites is discovered much more frequently than mechanical obstruction to the blood flow. Clinical experience also shows that ascites is simply one of the signs of general metabolic disorders in patients with hepatoma. Oedema of the subcutaneous tissue, transudate in the pleural cavities, and other clinical manifestations of the syndrome of increased protein loss in the gastro-intestinal tract appear before ascites. Disorders of protein and water-electrolyte metabolism become obvious only in the terminal stage of hepatoma, usually four to six months after the appearance of its first symptoms.

Metastatic spread to the portal lymph nodes is rare in cases of hepatoma; jaundice is usually caused by necroses of the hepatic cells and not by bile drainage block, i.e. it is hepatocellular in origin. It develops in concomitance with hepatomegaly, as a rule, and is rarely intensive. Cholangiomas commonly arise from the epithelium of ducts stretching close to the hepatic porta and because of this they set in in most cases with the obstructive jaundice syndrome which tends to progress rapidly.

In summing up it may be stated that in hepatoma jaundice always joins hepatomegaly, develops slowly, and is not intensive as a rule. Fever appears before jaundice. Jaundice is usually the first sign of cholangioma, it intensifies rapidly and total discoloration of the stool may occur. Intensive jaundice in primary carcinoma of the liver always arises under the effect of mechanical factors: escape of the liquefied hepatoma node into the biliary tract or compression of the biliary ducts by the growing tumour.

Hepatoma with multicentral growth is encountered about twice as often as all the other hepatomas taken together. In most cases it develops in concomitance with some other chronic disease of the liver (cirrhosis, haemachromatosis, syphilis, and parasitic diseases) as if becoming its terminal stage. The development of carcinoma in attendance to such chronic cirrhosis is diagnosed because of pain in the region of the liver and the rapid deterioration in the patient's general condition for which there seems to be no cause.

Developing in attendance to latent chronic hepatitis or cirrhosis, hepatoma with multicentral growth sometimes leads to cachexia and death before hepatomegaly has time to develop.

Multilobular hepatoma in a cirrhotic liver is combined with splenomegaly much more frequently and complicated by ascites and anasarca much earlier than hepatoma arising from a single node in a patient with no cirrhosis of the liver. This is explained by the existence of marked disorders of protein metabolism in cirrhosis when carcinoma has still not developed. The syndrome of increased protein losses into the gastro-intestinal tract in carcinoma simply promotes the development of cachexia and hypoproteinaemic oedema.

The systemic manifestations of primary carcinoma of the liver are no different in principle from those of cirrhosis, and should therefore be used with immense caution for the purpose of differential diagnosis.

Laboratory tests are of great assistance in the diagnosis of primary carcinoma of the liver. Just as other focal hepatic lesions, hepatoma is marked by increased alkaline phosphatase activity. Damage caused to the parenchyma of the organ by growing tumour leads to hyperbilirubinaemia and increased transaminase activity. It has been established in recent years that specific globulin is found in the blood of approximately 90 per cent of patients suffering from primary carcinoma of the liver. Although α_1-fetoprotein is also found in other diseases, its identification in a patient with a tentative diagnosis of hepatoma indicates the need to search for a tumour by means of other methods.

The results of isotope and echographic scanning of the liver show the approximate localization of the tumour but do not allow primary carcinoma to be distinguished from metastatic carcinoma. Laparoscopy with biopsy of several hepatic areas makes it possible to diagnose tumours which have reached the surface of the liver in their growth. Hepatic arteriography and splenoportography help to reveal and localize the hepatoma as well as to distinguish it from tumours of other organs.

The results of simple and generally accessible methods of examination such as the appraisal of changes in the composition of the red and white blood are also of high differential diagnostic signifi-

cance. Primary carcinoma of the liver is marked by moderate leucocytosis and moderate anaemia. Severe anaemia is usually not encountered, whereas in 4.0 to 9.6 per cent of cases even erythrocytosis is disclosed.

Primary carcinoma of the liver, as malignant tumours of other localization, is complicated by the syndrome of increased protein losses into the gastro-intestinal tract and the syndrome of intracellular protein catabolism. As a consequence, hypoproteinaemia develops mainly due to a decrease in the blood albumin concentration.

The clinical picture of most cases of primary hepatoma is so peculiar that the diagnosis can be made at the patient's bedside. Unfortunately, this is not true of its rarer or complicated forms the diagnosis of which often proves possible only after considerable logical and technical difficulties have been coped with.

Metastatic carcinoma of the liver. Metastatic carcinoma of the liver is encountered much more frequently than hepatoma and just as the latter, it may grow multicentrally, diffusely or as a single large tumour. Carcinoma of the bronchus, stomach, pancreas or mammary gland is the most common source of metastasis.

Quite often when there is no question that the patient has metastatic carcinoma of the liver, the primary tumour remains asymptomatic. Metastasis in the liver may sometimes become evident 20 to 30 years after the primary tumour has been removed. This happens particularly regularly in mammary carcinoma and melanoma of the eye.

About half the patients with latent metastatic carcinoma of the liver come to the doctor because of pain in the right hypochondrium which is attributed to stretching of the Glisson capsule or to focal perihepatitis. This explains the radiation of pain under the right shoulder blade and its intensification in deep respiration or cough.

Hepatomegaly and increased alkaline phosphatase activity in blood are found in the early stages of metastatic carcinoma. Jaundice, loss in body weight, and anaemia develop in addition to these signs in the late stages of the disease in about 50 per cent of cases. Metastases in the form of occasional nodes are found most often in the liver. Necroses occur in the centre of these nodes and their resolution is attended by fever and leucocytosis. Nodes located under the hepatic capsule are palpable. Signs of portal hypertension (splenomegaly, ascites and dilatation of the oesophageal veins) develop in approximately 20 to 30 per cent of cases.

In discussing the differential diagnosis between metastatic and primary carcinomas of the liver it is necessary before all else to study the medical history. Surgery undergone previously for a tumour of the stomach or some other organ is evidence in favour of

metastatic carcinoma. Negative results of the search for the primary tumour reduce the possibility of metastatic carcinoma of the liver, but do not rule it out completely.

Severe jaundice is often observed in metastatic carcinoma of the liver. Hepatoma is usually attended by moderate jaundice. Considerable enlargement of the left hepatic lobe is often met with in metastatic carcinoma but is a rare sign of hepatoma. Moderate tenderness of an enlarged liver in hepatoma has been pointed out above. Sharp spontaneous pain or tenderness of the liver elicited by palpation is characteristic of metastatic carcinoma.

Primary and metastatic carcinomas of the liver are usually marked by moderate anaemia, but erythrocytosis is observed only in hepatoma. Alpha-fetoglobulin is found in 90 per cent of patients with hepatoma; it is sometimes detected in carcinoma of the stomach with metastatic spread to the liver, but is never found when the primary carcinoma is of some other localization.

The metastatic tumour is of the same structure as the primary tumour, so that hepatoma may be distinguished from metastatic growth by histological examination in most cases. The material for histological examination is obtained either by needle biopsy or by selective biopsy carried out during laparoscopy. The last method possesses many advantages. It provides for collecting tissue from several hepatic areas and appraising the external appearance of the organ and the tumour nodes accessible to inspection. Characteristic umbilical-like depressions are often seen on the apex of metastatic nodes.

We have no specific tests to date which could help in identifying metastatic carcinoma of the liver. Scanning of the liver, laparoscopy and laparotomy are the most valuable diagnostic methods. Up to 84 per cent of metastases on the surface of the liver may be detected by laparoscopy. Metastases lying deep and those on the posterior surface of the liver escape detection by this method. Scanning of the liver with gold and technetium isotopes reveals up to 83 and 79.9 per cent of metastases, respectively. Only metastases of more than 2 cm in diameter may be demonstrated by either of these two methods. Laparotomy reveals all the metastases within view growing on the surface and some of the deeply lying metastases. Metastases could not be demonstrated by this method in 5 to 14 per cent of patients. With the simultaneous use of several methods, approximately 90 per cent of all cases of metastatic carcinoma of the liver can be detected.

Benign tumours of the liver are asymptomatic as a rule. For reasons as yet unknown they begin growing larger at times. This usually happens in middle-aged females. Growth of the tumour is accompanied by enlargement of the abdomen. Hepatomegaly develops if the tumours are growing inside the liver or on its surface.

A pedicled tumour may compress the adjoining organs and cause disturbances in their function.

Palpation reveals a non-tender tumour usually with an even surface and a soft-elastic consistency. Most benign tumours are located in the epigastrium or right upper abdominal quadrant. Despite the fact that some tumours are extremely large the patient's general condition is satisfactory.

If the tumour is a haemangioma, a continuous murmur is often heard over it and becomes noticeably intensified when compressed with a phonendoscope. Scout radiograph of the abdomen shows an enlarged liver sometimes with calcified areas. In character this calcification noticeably differs from that developing along the outline of a hydatid cyst and within metastatic carcinoma and sarcoma.

Scanograms demonstrate an avascular benign tumour as a cold zone and a haemangioma as a zone of increased isotope concentration. Ultrasonic scanning of the liver distinguishes a massive tumour from a cyst and haemangioma. The results of laparoscopy, which may be supplemented by biopsy if the need arises, are of particularly high diagnostic significance. The location and contours of the tumour are also clearly demonstrated on radiographs taken after pneumoperitoneum is produced.

A tentative diagnosis of a benign tumour may be made if the new growth has long existed in a person without signs of ill health and with no changes in the blood composition. The final diagnosis is based on the results of histological examination. Haemangiomas (just as necrotized malignant tumours) are sometimes complicated by haemorrhage into the peritoneal cavity and great care should always be exercised in performing diagnostic biopsy of tumours.

Other cysts and tumours of the liver. Hepatomegaly is a constant sign of *sarcoma of the liver* which is a rare disease and is mainly encountered in young persons. Sarcoma is usually found in the right lobe of the liver. It is palpated as a firm elastic tumour with an uneven surface. Diffuse enlargement of the liver is encountered in rare cases.

The central part of the tumour is continually subject to melting with the formation of an abscess. Damage to the hepatic parenchyma adjacent to the abscess leads to jaundice. This happens only in the late stages of the disease. Absorption of the disintegration products is attended by fever and leucocytosis. Eosinophilia is a frequent occurrence. The contents of the cysts formed in the centre of the tumour sometimes rupture into the abdominal cavity. Acute peritonitis develops in such cases (as in rupture of melted primary carcinoma of the liver into the abdominal cavity).

The clinical picture of primary sarcoma of the liver resembles the picture of its pyogenic abscess or a suppurated hydatid cyst

from which it must be differentiated. All three diseases are marked by hepatomegaly and fever and are often complicated by jaundice. Despite the underlined similarities the differential diagnosis between them presents no difficulty in most cases.

In our long years of practice, we encountered primary *melanoma* (melanosarcoma) of the liver only twice. In all other cases the tumour was metastatic.

Melanoma metastases to the liver sometimes arise a considerable length of time after the removal of the primary tumour of the eye or skin. The tumour is black and grows as a single node or a conglomerate of nodes. A liver involved in a melanoma has a nodular surface and a sharp and firm border. Ascites and splenomegaly appear just before death, which usually occurs one to six months after the discovery of hepatomegaly.

The diagnosis of metastatic melanoma of the liver is quite probable if it is found that the patient had been operated on earlier for a pigmented tumour of the eye or skin. The diagnosis may be verified by examining the urine for melanin. Freshly passed urine of these patients has a normal colour, but it turns black if left in the open air. It is typical that only the upper layers of the urine turn black at first, but when any oxidizer is added all the urine becomes black. Dark brown or black urine is also encountered in alkaptonuria, tyrosinosis, ochronosis and some other diseases.

Diseases of the Hepatic Vessels

This chapter deals with the differential diagnosis of diseases whose clinical picture is always marked by hepatomegaly and splenomegaly. After Mansurov (4965) who provided the first exhaustive description of diseases of the hepatic vessels, we excluded diseases of the hepatic artery from our discussion because they are not attended by enlargement of the liver. Diseases of the portal and hepatic veins are quite rare, but, unfortunately, they are often discussed only at clinical-pathological conferences devoted to misdiagnosed cases. This is explained by the fact that most patients suffering from diseases of the hepatic vessels are brought to the town hospital in ambulances as emergency cases with signs of massive gastro-intestinal haemorrhage. The very first haemorrhage of this kind occurring in a person apparently in sound health proves to be fatal in about half of such cases. Because of the patient's brief hospital stay the doctor lacks time and often, due to the severity of the condition, lacks the possibility of examining the patient properly. Most diseases of the hepatic vessels have to be differentiated from cirrhosis of the liver.

Thrombosis of the portal vein. Acute thrombosis of the portal

vein is encountered in patients with cirrhosis of the liver. Signs of thrombosis of the portal vein suffered in the past are found in approximately 10 per cent of patients with cirrhosis. The following conditions predispose to the formation of thrombi in the portal vein: inflammatory changes in its walls, changes in the blood coagulation properties, decelerated rate of blood flow.

Acute thrombosis of the portal vein with its total obstruction is sometimes observed in pylephlebitis, pyogenic abscess in the hepatic porta, and septic embolisms. Sometimes it is the terminal stage of gradual obstruction of the portal vein or its branches by a growing tumour or small recurrent thrombi.

Thrombosis of the portal vein or its branches should be considered in all cases of sudden pain in the epigastrium attended by drastic abdominal distension, rapid accumulation of fluid in the peritoneal cavity, and repeated vomiting. In a patient with cirrhosis the vomit may be bloody. Thrombosis usually sets in after mild injury to the abdomen and often terminates in death from intestinal necrosis.

Thrombosis of some branches of the portal vein has a less dramatic picture. Dull pain in the region of the liver or the right hypochondrium is felt for one or two days and then gradually disappears. Moderate leucocytosis and increase of body temperature to a subfebrile level are sometimes encountered during the pain.

As far as it is possible to judge from the results of splenoportography and the findings of operations and autopsies, some of the thrombi ultimately undergo recanalization. It is possible that in some cases parietal thrombi form from the very onset and narrow the vascular lumen but do not obstruct it completely.

Long-term follow-up with regular comprehensive examination of patients suffering from polycythaemia shows that recurrent thromboses of some branches of the portal vein lead to the formation of portal hypertension. More or less intense pain in the region of the liver appears in these patients now and then. The spleen becomes gradually enlarged. Ascites develops sometimes, always making the physician doubt whether it is a consequence of portal hypertension or of heart failure.

A peculiar clinical picture develops in incomplete thrombosis of the portal vein system with prevalent involvement of the splenic vein. Enlargement of the spleen in such cases is accompanied by hypersplenism: anaemia, leucopenia and thrombocytopenia. In affection of just the splenic vein, the liver is normal in size and signs of its functional deficiency do not develop. Enlargement of the liver is evidence of simultaneous affection of the intrahepatic branches of the portal vein. Even in such cases, however, ascites and jaundice rarely develop, and splenomegaly predominates in the clinical picture. The oesophageal veins are always dilated.

In such cases portal hypertension usually begins with extraordinarily massive bloody vomiting in a person who seems to be in sound health. In about half the cases the very first gastro-intestinal haemorrhage proves fatal. If the patient survives the first haemorrhage, a second haemorrhage, just as massive, occurs in a few years.

Pylephlebitis. Besides cirrhosis and polycythaemia incomplete (parietal) thromboses of the portal vein also occur in haemolytic anaemia and in compression of its branches with tumours or their metastases. All diseases marked by a decelerated blood flow through the liver (endophlebitis of the hepatic veins, veno-occlusive disease, tumours and abscesses of the liver, impaired flow of blood from the liver in right-ventricular failure, constrictive pericarditis and thrombosis of vena cava inferior distal to the site where the hepatic veins enter it) are conducive to the development of thrombosis. Pylephlebitis is nevertheless the most common cause of thromboses in the portal vein system. It is now a rare disease. Clinically manifested pylephlebitis is usually encountered by surgeons. Internists only have to deal with flaccid variants of this disease and with its consequences among which portal hypertension is the principal abnormality.

Pylephlebitis commonly develops in attendance to some other disease. It is particularly often a complication of sepsis, appendicitis, cholecystitis, ulcerative colitis, Crohn's disease, diverticulitis, and exacerbation of haemorrhoids. Pylephlebitis quite often develops as a complication of abscess of the liver, cholangitis, pancreatitis, inflammation of the female and male genitals, mesadenitis, and paranephritis. Any operation on the abdominal organs may be complicated by pylephlebitis.

The clinical picture of pylephlebitis is diverse. In severe cases the patient has recurrent chills attended by profuse sweating, high temperature, and pain in the right upper abdominal quadrant. Disturbance in the patient's general condition, the size of the liver, the degree of jaundice, and the extent of involvement of the diaphragm and spleen in the process are determined by the severity of the infection. Milder cases are characterized by subfebrile temperature and subicteric sclerae and mucous membranes; the liver is slightly enlarged and its border is soft and tender. The spleen is usually of normal size at the onset of the disease, but becomes enlarged when the disease is of a longer duration. In severer cases, abscesses form in the liver and the clinical picture cannot be differentiated from that of sepsis.

It is relatively easy to make the diagnosis of pylephlebitis when it develops in the wake of some acute surgical disease. Unfortunately, the principal disease may be very mild and is often not even diagnosed. Sometimes the causes of the moderate or even high fever in such cases remain unknown for a great length of time (the diag

nostic work in such cases is discussed in the chapter 'Fever of Unknown Origin').

With the development of hepatomegaly, it usually becomes necessary to distinguish pylephlebitis from abscess, primary tumour and a suppurative cyst of the liver. Repeated blood cultures for isolating the causative agent make it possible not only to identify the aetiology of the fever, but also to choose the most suitable antibiotic for the treatment.

The internist, as a rule, witnesses flaccidly developing forms of pylephlebitis. They are characterized by mild pain in the region of the liver, moderate leucocytosis, and long-term subfebrile body temperature. The mildly enlarged liver is tender to palpation. In our cases with such forms of pylephlebitis the blood was sterile. The disease was usually misdiagnosed as chronic cholecysto-cholangitis, chronic appendicitis or some other chronic inflammatory disease of an internal organ.

The cause of the fever usually becomes obvious only after a long period of observation during which splenomegaly and signs of more or less developed collateral circulation appear. The final diagnosis in such cases is based on the results of splenoportography which reveals portal hypertension and signs of stenosis or obstruction of some branches of the portal vein.

Primary portal hypertension (Banti's syndrome). The process of obliteration beginning in the umbilical vein after its ligation sometimes spreads to the portal vein. Congenital stenosis of the portal vein develops either as an isolated abnormality or in combination with other anomalies of the vein. The stenosis may occur only in some segments of the small branchings of the portal vein or all its main branches may be involved.

In modern literature, the clinical picture of sclerosis of the intrahepatic branchings of the portal vein is designated 'Banti's syndrome' or 'hepatoportal sclerosis'. While it is no different from portal hypertension of other origin, it noticeably differs in the methods of treatment.

Phlebosclerosis rates second among the congenital anomalies of the portal vein system in practical significance. The clinical manifestations of this anomaly are also described as Banti's syndrome, or 'idiopathic portal hypertension'. Its underlying factor is hypertrophy of the muscular coat of the portal vein with the formation of trabeculae on its wall. In most cases, only some segments of the portal vein are affected. In rare cases practically all its branches are involved.

Portal vein segments distal to the sites of the stenoses are noticeably dilated and tortuous. Portal hypertension is manifested by considerable enlargement of the spleen and hypersplenism. Simultaneous enlargement of the liver often occurs. As in the other cases

of Banti's syndrome, collateral circulation forms mainly in the veins of the distal oesophagus and cardia. Massive gastro-intestinal bleeding often proves to be the first complication calling for comprehensive examination of the patient.

Secondary portal hypertension. Severe stenosis of the portal vein branches always leads to the development of portal hypertension. The condition is called secondary portal hypertension when the cause of the stenosis has been identified. Organs located distally to the sites of the stenosis are drained of blood through collaterals. Hepatomegaly and splenomegaly discovered many years after recovery from pylephlebitis is sometimes mistaken for chronic hepatitis or cirrhosis of the liver.

The differential diagnosis between the consequences of chronic portal hypertension and those of cirrhosis of the liver is made relatively easily at the patient's bedside if convincing data on the features of their course have been obtained.

Splenomegaly in Banti's syndrome develops in childhood unassociated with any disease suffered previously. In adolescence these patients already have an obvious clinical picture of portal hypertension. The spleen is always drastically enlarged and the liver is also enlarged in most cases. The clinical picture of marked portal hypertension at both young and mature age may be a manifestation of a disease of the portal vein or liver terminating in cirrhosis.

Detailed questioning about past diseases and their complications may be of essential aid in identifying the cause of the malady. As it is pointed out above, pylephlebitis may be a complication of many infectious diseases and injuries to organs located in the abdominal cavity. Quite often it may also be among the complications developing after operation on the abdominal organs.

Patients with cirrhosis of the liver often have a history of jaundice and sometimes of abuse of alcohol. Persistent subfebrile temperature of no obvious cause should rather be regarded as evidence of pylephlebitis suffered in the past.

Attention should likewise be focused at the functional state of the liver and the size of the spleen. Disorders of hepatic function (hypoalbuminaemia, high transaminase activity, etc.) testify in favour of cirrhosis. In chronic thrombosis of the portal vein, i.e in portal hypertension with no concomitant cirrhosis, liver function is usually quite satisfactory. The spleen in cirrhosis may be normal in size or enlarged. In chronic portal vein thrombosis it is always enlarged.

In cirrhosis, the scanograms always demonstrate increased uptake of the radioactive indicator both by the spleen and the bone marrow; in portal hypertension with no attendant cirrhosis enlargement of only the spleen is demonstrated, while the uptake of the radioactive indicator by the bone marrow is normal.

Systemic manifestations of cirrhosis are never encountered in chronic portal vein thrombosis. Gastro-intestinal haemorrhage is usually one of the first grave complications of this disease. Disorders of water-electrolyte metabolism in cirrhosis almost always precede bleeding from the oesophageal veins. In portal hypertension, gastro-intestinal haemorrhage occurs in no association with disorders of water-electrolyte metabolism. Patients with chronic portal vein thrombosis die from haemorrhage, as a rule, while patients with cirrhosis die from hepatic failure.

The final diagnosis may always be established from the results of laparoscopy with biopsy of chosen hepatic areas and from the findings of splenoportography. These methods make it possible to appraise the external appearance of the liver and spleen, the morphological structure of the liver and the extent of portal hypertension and collateral circulation.

Thrombosis and inflammation of the hepatic veins (the Budd-Chiari syndrome). Obstruction of the hepatic veins as the result of inflammation or thrombosis is called the Budd-Chiari syndrome. It develops most frequently in polycythaemia, haemolytic anaemia crises, and in primary and metastatic tumours of the liver. The hepatic veins are sometimes involved in an inflammatory process in abscess of the liver, cholecystitis, injury to the liver, cirrhosis and pregnancy. Thrombosis of the hepatic veins has been described in prolonged use of oral contraceptives and in abuse of alcohol. It is encountered from time to time in inflammatory diseases and tumours of the kidneys, lungs, pancreas and other organs. Many toxic substances of bacterial and plant origin also cause injury to the intima which is complicated by thrombosis of the hepatic veins.

The clinical manifestations of the Budd-Chiari syndrome are determined by the extent and rate of thrombosis development. The pain syndrome predominates in the clinical picture of acute thrombosis of the hepatic veins. Severe pain in the right hypochondrium and right infrascapular region caused by stretching of the Glisson capsule may lead to shock and death. In less graver cases, rapid enlargement of the liver and formation of ascites are encountered simultaneously with the pain.

The patient's fate is determined by the rate of the formation of collaterals between veins stretching in the Glisson capsule and veins of the organs adjoining it and by the volume of the collateral circulation. Clinical experience shows that acute thrombosis of the hepatic veins usually takes an unfavourable course. Death occurs in a few hours or weeks. In the acute period death is caused by shock, in a later period by hepatic failure or gastro-intestinal bleeding from the collaterals.

Acute thrombosis of the hepatic veins and acute thrombosis of the portal vein are characterized by the sudden appearance of ab-

dominal pains and rapid development of ascites. Both diseases may be complicated by gastro-intestinal bleeding and shock. They differ sharply from each other in the character of changes in the liver. In acute thrombosis of the portal vein the liver may be enlarged or of normal size. It does not change in size noticeably during the disease, and may even grow somewhat smaller during shock or gastro-intestinal bleeding. In thrombosis of the hepatic veins, the liver grows continuously in size and its border becomes tender to palpation.

Incomplete thrombosis of the hepatic veins usually takes the course of a chronic disease, the main signs of which are gradually progressive hepatomegaly, ascites and splenomegaly. The rate of liver enlargement and the degree of its tenderness are mainly determined by the rate of obliteration of the sum-total lumen of the hepatic veins and the rate of the development of collateral pathways along which blood flows from the liver. The pronounced character of these processes also depends on the functional state of the liver prior to the disease. Circulatory disorders in the liver are often complicated by its necroses leading to the development of hyperbilirubinaemia and increased transaminase activity. Portal hypertension and splenomegaly are often encountered.

The disease follows a chronic course and the clinical picture gradually takes on a resemblance to that of cirrhosis of the liver. This resemblance becomes all the more significant the sharper portal hypertension is manifested. Some differences are nevertheless detected in the localization and degree of formation of the anastomoses. The network of varicose subcutaneous vessels is less pronounced in cirrhosis than in the Budd-Chiari syndrome. This is explained by the frequent combination of chronic thrombosis of the hepatic veins with parietal thrombosis of vena cava inferior usually developing where it is continuous with the hepatic veins.

In such cases, both portocaval anastomoses characteristic of cirrhosis and cavacaval anastomoses typical of chronic vena cava thrombosis are found in the patient. Anastomoses of the first type are arranged around the umbilicus and blood in them flows in the caudal direction. The network of cavacaval anastomoses forms mainly on the lateral surfaces of the anterior chest wall and abdomen and blood in them flows cranially. The cavacaval anastomoses are usually manifested more clearly than the portocaval.

The final diagnosis is established from the results of special methods of examination. The extraordinarily developed collateral circulation of the subcutaneous vessels on the anterior surface of the body is accepted as the main indication for conducting splenoportography and cavagraphy and for measuring blood pressure in the hepatic veins. Splenoportography is particularly valuable in revealing the conditions of blood flow in the branches of the portal vein.

In the Budd-Chiari syndrome, the splenic vein and other branches of the portal vein are never obstructed. It often proves impossible to advance a catheter into the hepatic veins in this syndrome. Stenosis and sometimes obliteration of vena cava inferior are also encountered in such cases. Pressure in the post-sinusoidal vessels is normal in thrombosis of the portal vein but is always increased in intrahepatic obstacles to the blood flow.

Veno-occlusive disease. In the past 20-25 years ever-increasing interest has been aroused in partial or total obliteration of small (central lobular and sublobular) hepatic veins which is characterized by necrobiotic changes in the adjacent areas of the hepatic lobule. With the gradual development of perivascular fibrosis the drainage of the hepatic sinusoids of blood becomes more and more difficult and hepatomegaly develops, which is soon joined by ascites and oedema of the shins. The clinical picture of cirrhosis eventually develops with more or less marked signs of portal hypertension. Enlargement of the spleen becomes quite noticeable and a network of subcutaneous collaterals develops.

Depending on the rate of its development, veno-occlusive disease may terminate in death from hepatic coma or in recovery, which is rarely total. One or two years, sometimes a few months after disappearance of the oedema and ascites, progressive hepatomegaly and splenomegaly occur and hypoalbuminaemia, ascites and dilated veins on the anterior surface of the abdomen and chest appear. The progressive cirrhosis may be complicated by gastro-intestinal bleeding or hepatic insufficiency.

Veno-occlusive disease is encountered most frequently among children. It was established that the disease became widespread during the postwar years. Its development is associated with the effect of toxins of plant origin. It has recently been found that the disease may be caused by exposure to radioactive agents. It is very often encountered among workers employed in chlorvinyl production.

Diseases of the Blood and Haematopoietic Organs

Hepatomegaly and splenomegaly are encountered in most diseases of the blood and haematopoietic organs. In most of the clinical forms of these diseases, the final diagnosis may only be made after examination of blood and bone marrow smears. Although the suggestion voiced by some authors (Kawai, 1973) to group diseases of the blood according to a purely morphological principle (myeloproliferative, lymphoproliferative, etc.) is logically irreproach-

able, it is nevertheless unacceptable for the clinician who must make the preliminary diagnosis at the patient's bedside on the basis of the results of clinical examination.

In the opinion of the author, the grouping of diseases of the blood and haematopoietic organs into acute and chronic according to their clinical course accepted in the Soviet Union is more suited to the specific features of the physician's differential diagnostic work.

Acute leukaemia. Hepatomegaly and splenomegaly are not among the constant signs of acute leukaemia. The border of these enlarged organs is usually soft and non-tender. Moderate enlargement of the spleen is encountered more often in lymphoid leukaemia than in myeloid leukaemia. A considerably enlarged spleen with a firm rounded border in a patient with predominance of myeloblasts in blood is typical of exacerbation of chronic myeloid leukaemia.

Acute leukaemia usually begins (in about 60 per cent of cases) as anaemia consequent upon suppressed erythropoiesis. Much less frequently the disease sets in as an acute respiratory infection which is soon complicated by tonsillitis, or as purpura caused by thrombocytopenia. In rare cases acute leukaemia beginning with fever and pain in the bones and joints may be misdiagnosed as rheumatic fever. Pain in the bones and joints is explained by infiltration of the synovial membranes or periosteum with leukaemoid tissue. The diseases mentioned are easily distinguished from acute leukaemia by the results of examination of peripheral blood or bone marrow.

Abnormalities in the number and quality of the leucocytes is a characteristic sign of acute leukaemia. The leucocyte count may be either drastically reduced or considerably increased. The appearance of blast cells is particularly typical of leukaemia. In extremely marked leucopenia, the qualitative composition of the leucocytes is studied after the blood had been centrifuged. More reliable findings are obtained by sternal puncture. Infiltration of the bone marrow by blast cells is typical of leukaemia.

The difference in the prognosis and therapeutic methods makes the exact diagnosis of the different forms of acute leukaemia essential. Sometimes their diagnosis cannot be made with confidence from the results of the clinical examination and morphological study of the different cells stained by routine methods. In such cases the leukaemia may be classified by means of electron microscopy of leucocytes, leukaemic cell cultures or by cytochemical methods. Detailed interpretation of the results is the task of cytochemists.

Acute leukaemia usually must be differentiated from acute aplastic anaemia, infectious mononucleosis, and leukaemoid reaction.

Infectious mononucleosis may be marked by long-term fever, necrotic tonsillitis, and enlargement of the liver, spleen and lymph

nodes. Leucopenia is sometimes found in the initial stages of the disease and leucocytosis with atypical lymphocytes in the late stages. In distinction from acute leukaemia, infectious monocytosis is not attended by anaemia or thrombocytopenia. Blast cells are distinguished by uniform structure in acute leukaemia, but are never monotypical in infectious mononucleosis. They always differ one from the other in tinctorial properties.

The diagnosis of infectious mononucleosis is confirmed by a positive Paul-Bunnell test (heterophilic agglutination) in a titre of no lower than 1:224. The differential absorption test suggested by Davidsohn is more specific. The final diagnosis may sometimes be established only from the results of bone marrow examination.

It is more difficult to differentiate acute leukaemia from *aplastic anaemia* with foci of proliferation of non-differentiated cells in the bone marrow. Fever, anaemia, leucopenia, thrombocytopenia and purpura may develop in both diseases. In distinction from aplastic anaemia acute leukaemia is often marked by enlargement (even if insignificant) of the liver and spleen. The submandibular lymph nodes may be enlarged in both diseases as a consequence of concomitant tonsillitis. In all other cases this enlargement should be accepted as evidence in favour of acute leukaemia. The same significance should be attached to enlargement of the lymph nodes in other parts of the body.

Trephination biopsy is resorted to in cases which are more difficult because the bone marrow aspirate may not provide the basis for the final diagnosis. In some cases the diagnosis is established only from the results of a longer follow-up of the disease and from the findings of repeated sternal puncture and trephination biopsy.

The differential diagnosis between acute leukaemia and *leukaemoid reaction* is easily made. The leukaemoid reaction always joins some other disease which is usually of an infectious nature or it develops as a reaction to some drugs. It is distinguished by a very brief course. Complications characteristic of acute leukaemia (leukaemoid infiltrate in the tissue, involvement of the liver, spleen, bone marrow, lymph nodes and the central nervous system in the process) never develop in it.

Blast cells are found in the peripheral blood and bone marrow only in acute leukaemia, but are absent in leukaemoid reaction. The correct diagnosis is usually made from the results of bone marrow examination. A certain amount of caution should be exercised only in disseminated tuberculosis and disseminated histoplasmosis.

Chronic myeloid leukaemia. In chronic myeloid leukaemia the liver is usually enlarged but rarely to a large size. Enlargement of

the spleen which is firm and non-tender predominates in the clinical picture. It gradually grows and often occupies the entire left half of the abdominal cavity. Moderate enlargement of the lymph nodes is sometimes encountered. The disease begins insidiously and splenomegaly and hepatomegaly are already found when the patient applies to the doctor for the first time. Enlargement of the spleen may be discovered by chance during regular screening or in examination of the patient for some other disease.

In our experience, chronic myeloid leukaemia usually began with purpura or anaemia. Other authors point out that patients with chronic myeloid leukaemia usually come to the doctor with complaints of heaviness in the left hypochondrium. At the later stages, the disease sometimes begins with irregular fever and pains in the left hypochondrium, left side and left subclavicular region. These pains are attributed to infarction of the spleen.

The underlying factor of the disease is irrepressibly progressive proliferation of the bone marrow myeloid germ in combination with the formation of foci of extramedullary haematopoiesis and leukaemoid infiltrates in different organs. Cytogenetic analysis reveals the Phyladelphia chromosome in 70 to 95 per cent of cases of chronic myeloid leukaemia. An increased content of vitamin B_{12} and uric acid is always detected in the blood.

The blood leucocyte count sharply increases and may be as high as $3 \cdot 10^5$ μl. Immature forms of granulocytes (juvenile, myelocytes, a small number of promyeloblasts and myeloblasts) and slightly enlarged number of basophils and eosinophils are discovered in the smear. The blood platelet count may be increased in the developed stage of the disease, but is reduced in the terminal stage as a rule. Myeloid hyperplasia is disclosed in the aspired bone marrow.

The development into the terminal stage may be determined because of the progressive enlargement of the spleen, the appearance of anaemia, thrombocytopenia and purpura, an increase in the blood basophil count and the appearance of fever for which there seems to be no cause. A progressive increase in the number of blasts in the blood and bone marrow within a few months is the most characteristic feature. Patients die from advancing anaemia, haemorrhages and concomitant infection often of fungus origin.

It is most difficult to differentiate chronic myeloid leukaemia from benign subleukaemic myelosis (myelofibrosis, osteomyelosclerosis) which is also characterized by splenomegaly, anaemia, the presence of normoblasts and juvenile forms of granulocytes in the blood, and the formation of haematopoietic foci in the liver, spleen and some other organs. The absence of Philadelphia chromosome in patients with myelofibrosis allows this disease to be differentiated from chronic myeloid leukaemia.

Myelofibrosis usually sets in at elderly age. Its clinical manifestations may resemble those of chronic myelosis for a long time. Fever, splenomegaly, gastro-intestinal haemorrhages and anaemia appear in the late stage. Patients sometimes have sharp pain in the limbs, thromboses of veins with recurrent embolisms in the pulmonary vessels, right-ventricular failure with oedema and ascites.

Only a few cells are sometimes recovered from these patients by sternal puncture. The main sign of the syndrome, fibrosis of the bone marrow, is discovered by means of trephination biopsy.

The patients usually die from concomitant infection, thromboembolism of the pulmonary artery, haemorrhages or heart failure. The development of chronic myeloid leukaemia with blast transformation has been described in these patients.

Enlargement of the liver and spleen is encountered almost in every case of **chronic lymphoid leukaemia.** Unfortunately, hepatomegaly and splenomegaly (like anaemia) are among the late manifestations of the disease. Chronic lymphoid leukaemia begins either with enlargement of the lymph nodes or with an increase in the leucocyte count. The lymph nodes of the neck are usually involved first. Less frequently, the disease begins with enlargement of the mediastinal lymph nodes. Inflammation of the lacrimal and salivary glands (Mikulicz's syndrome) sometimes develops in attendance to affection of the lymph nodes.

The laucocyte count ranges between $15 \cdot 10^3$ and $4 \cdot 10^5$ per 1 μl. Lymphocytosis is discovered long before the appearance of the first subjective disorders of health as a rule. An increase in the number of small lymphocytes is particularly characteristic.

The diagnosis of chronic lymphoid leukaemia is not difficult because its principal signs (lymphadenopathy, lymphocytosis) are easily disclosed during routine examination of the patient. The final diagnosis is established from the results of bone marrow examination, although Leavel and Thorup (1976) claim that this is unnecessary in many cases.

Chronic lymphoid leukaemia is distinguished from *infectious mononucleosis* by the morphology of the cells. In infectious mononucleosis the lymphocytes and monocytes differ noticeably in size and shape. The presence in the blood smear of many large cells is considered a particularly characteristic feature. In lymphoid leukaemia small lymphocytes predominate, which sometimes may account for 98 per cent of the total lymphocyte count during exacerbation of the disease. Study of the aspirated bone marrow specimen allows chronic lymphoid leukaemia to be easily distinguished from infectious lymphocytosis (lymphocytic type leukaemoid reaction).

The term 'leukaemic reticuloendotheliosis' formerly designated a rare form of chronic lymphoid leukosis, hairy cell leukaemia. The disease usually begins at a younger age than chronic lymphoid leukaemia. The main sign of the disease is splenomegaly and the presence in the blood and bone marrow of characteristic cells differing from lymphocytes in the structure of the nuclear chromatin and the presence of villose cytoplasmic projections. Leucopenia, neutropenia in particular, is found in almost every case.

The disease is complicated by some infection when leucopenia becomes very manifest. The advancement of the disease leads to anaemia and thrombocytopenia. Moderate lymphadenopathy is very rare. The patients survive three to five years (after splenectomy).

The final diagnosis is made when acid phosphatase resistant to tartaric acid is found in the lymph cells.

Macroglobulinaemia. In 1944 Waldenström published the results of observations over two patients with hepatomegaly, splenomegaly, lymphadenopathy and a high content in the blood of monoclonic macroglobulin which may be encountered rarely in other forms of leukaemia, haematosarcoma and immunodeficient states.

The underlying factor of the disease is irrepressible proliferation of plasmocytes and lymphocytes producing type M immunoglobulins. These cells infiltrate the bone marrow and are found in the spleen, liver and lymph nodes.

The disease is mostly encountered among elderly and aged males. The disease begins with loss in body weight which is soon joined by purpura and less frequently by Raynaud's syndrome. Some authors claim that paroxysmal haemoglobinuria from cold is a variant of macroglobulinaemia. Anaemia, hepatomegaly and splenomegaly are observed in the later stages of the disease. The peripheral lymph nodes are usually moderately enlarged, the retroperitoneal lymph nodes are sometimes very large. Death usually occurs from concomitant infection.

Increased concentration of monoclonic immunoglobulins in the blood leads to changes in its physico-chemical properties. The erythrocyte sedimentation rate, blood viscosity and the tendency of the red cells to form rouleaux are sharply increased. The increased blood viscosity is clinically manifested by haemorrhages from the small vessels of the mucous membranes and retina, dizziness, convulsive seizures, and heart failure.

The solubility of monoclonic immunoglobulins changes sharply when water or some other substance is added to the serum or when the temperature of the serum changes. Gelatinization of the serum cooled to 0-4°C (cryoprecipitation) is encountered particularly often. It is believed that cryoglobulins are immune complexes under the effect of which the main clinical symptoms and signs of

the disease (purpura, Raynaud's syndrome, anaemia) develop. The clinical importance of pyroglobulins, i.e. immunoglobulins sharply changing their physico-chemical properties in elevation of body temperature, has been less studied.

Waldenström's macroglobulinaemia differs from *chronic lymphoid leukaemia* in the characteristic cell protein production and lymph cell polymorphism. Macroglobulinaemia is distinguished from *multiple myeloma* by the cellular substrate and rarer bone destruction. Its differentiation from other forms of paraproteinaemic haemoblastosis is far more difficult. Waldenström's macroglobulinaemia is usually characterized by a high serum immunoglobulin M content in normal content of immunoglobulins G and A, and by hyperproteinaemia and proteinuria.

Supplement XVI-1

Hepatomegaly and Splenomegaly

1. Acute anicteric hepatitis.
2. Chronic hepatitis.
   - Chronic benign (persistent) hepatitis.
   - Post-hepatitic syndrome.
   - Post-hepatitic hyperbilirubinaemia.
   - Chronic active hepatitis.
   - Fatty infiltration of the liver.
   - Gilbert's syndrome (disease).
   - Pericholangitis.
   - Hepatolenticular degeneration.
   - Drug-induced (toxic) hepatitis.
3. Cirrhosis of the liver.
   - Alcoholic cirrhosis.
   - Biliary cirrhosis.
   - Congenital cirrhoses of the liver.
   - Haemochromatosis.
   - Hepatolenticular degeneration.
   - Alpha-1-antitrypsin deficiency.
   - Gaucher's disease.
4. Cysts and tumours of the liver.
   - Cysts of the liver.
   - Congenital cysts of the liver.
   - Echinococcosis (hydatid disease) of the liver.
     - Cystic.
     - Alveolar.
   - Tumours of the liver.
     - Primary carcinoma of the liver.
     - Metastatic carcinoma of the liver.
     - Benign tumours of the liver.
   - Other cysts and tumours of the liver.
     - Sarcoma of the liver.
     - Melanoma of the liver.
5. Diseases of the hepatic vessels.
   - Thrombosis of the portal vein.

Pylephlebitis.
Primary portal hypertension (Banti's syndrome).
Portal hypertension (secondary).
Thrombosis and inflammation of the hepatic veins (Budd-Chiari's syndrome).
Incomplete thrombosis of the hepatic veins.
Veno-occlusive disease.

6. Diseases of the blood and haematopoietic organs.
Acute leukaemia.
Infectious mononucleosis.
Aplastic anaemia.
Leukaemoid reaction.
Chronic myeloid leukaemia.
Myelofibrosis.
Chronic lymphoid leukaemia.
Hairy cell leukaemia.
Macroglobulinaemia.

Chapter XVII

Jaundice

Jaundice is a syndrome developing as a consequence of the accumulation in the blood of an excessive amount of bilirubin. In the clinic its diagnosis is made when the body tegmentum is coloured in various tinges of yellow.

Jaundice may be the earliest and sometimes the only visible sign of many internal diseases. In acute hepatitis and obstruction of the biliary tract the yellow colour of the sclerae is first to be discovered. Yellow colour of the mucous membranes is detected somewhat later and then yellow pigmentation of the skin on the proximal parts of the limbs. The palms and soles turn yellow last.

The intensity of jaundice is determined by the blood supply to the organ or tissue. This is particularly well illustrated in the case of skin scars which are always of a less intensity of yellow than the surrounding normal skin. Accumulating in the skin, bilirubin in combination with other pigments stains it light yellow with a reddish tinge. Later the bilirubin in the skin is oxidized to biliverdin and jaundice acquires a greenish tinge. In long-term jaundice the skin turns blackish. The examination of the patient thus makes it possible to ascertain the duration of the jaundice, which is very significant from the standpoint of differential diagnosis.

The staining of the skin by bilirubin and the products of its conversion has to be differentiated from its staining by other pigments. Yellow skin is often found in a person who consumes a large quantity of carotin-containing vegetables. An orange tinge often develops after eating lots of oranges, tangerines, and pumpkin. It is general knowledge that the skin turns yellow after medication with some chemical agents among which quinacrine is most common. Temporary staining of the skin with carotin pigments is easily distinguished from true jaundice and mention of this is made traditionally rather than it is necessary for meeting the requirement of differential diagnosis.

The great number of classifications of jaundice indicates that none of them is ideal. Experience of many years under conditions of a large urban hospital with its standard biochemical laboratory shows the expediency of separating all cases of jaundice into two types: that with accumulation of conjugated bilirubin in the blood and a type marked by the accumulation of unconjugated bilirubin. These types of jaundice are easily distinguished one from the other by

examining the urine for the content of bile pigment. Each of these two principal types is in turn separated into two forms, hepatogenic and non-hepatogenic (Supplement XVII-1).

Jaundice with Unconjugated Bilirubin

Bilirubin forms from haem released during the breakdown of a haemoglobin molecule. Approximately 300 mg of unconjugated bilirubin forms daily. Its content in the serum is determined by the balance between the rate of red cell destruction and the excretory capacity of the liver. The accelerated destruction of the red cells leads to the entry of large amounts of unconjugated bilirubin into the blood. An adult possesses a great excretory reserve of the liver. This is why even when large amounts of red cells are destroyed, the blood bilirubin content remains normal or is slightly increased for a short while. The excretory function in children is of much lower potentiality than that of adults and unconjugated hyperbilirubinaemia is therefore encountered among children more often.

An increased concentration of unconjugated bilirubin in the blood may be a consequence either of marked increase in the rate of haemoglobin breakdown (which is encountered in massive red blood cell haemolysis) or of disorders in the capacity of the liver to bind unconjugated bilirubin with glucuronic acid.

Non-hepatogenic (Haemolytic) Jaundice

Increased haemolysis, irrespective of its cause, always leads to a characteristic clinical triad: anaemia, jaundice, and splenomegaly. An increased number of reticulocytes is found in the peripheral blood indicating intensified activity of the bone marrow. Hyperplasia of the erythroid germ is always detected in the bone marrow aspirate of these patients. The urine and faeces contain an increased amount of urobilin and stercobilin. No bilirubin is detected in the urine. These signs are easily revealed and the diagnosis of haemolytic jaundice (anaemia) therefore usually presents no difficulties.

It is far more difficult to determine the type of haemolytic jaundice. Complicated haematological examination must be resorted to: determination of red cell life span, Coombs' test, electrophoretic study of the haemoglobin types, etc. It is necessary to perform these tests because specific therapeutic and prophylactic measures which at times save the patient's life and preserve his working capacity can be applied if the exact diagnosis is made.

Haemolytic syndromes are commonly separated into congenital and acquired (autoimmune) syndromes and those of unknown aetiology.

Congenital haemolytic jaundice is characterized by reduced osmotic resistance of the red cells and autohaemolysis in defibrinated blood (when it is incubated for 24 hours at a temperature of 37°C). Haemoglobin anomalies are usually revealed by blood electrophoresis, the anomalous form of the red cells may be identified by incubating them for 1 to 12 hours at a temperature of 37°C. Autoimmune jaundice is always marked by the formation of antibodies (warm and cold). The tentative diagnosis of drug-induced haemolytic jaundice is made when Heinz bodies are identified in the red cells and is often confirmed by the test for G-6-PD activity. The origin of paroxysmal nocturnal haemoglobinuria is not known to date.

Congenital (spherocytic) haemolytic jaundice. In this disease the red cell membrane is distinguished by abnormally high permeability to sodium ions which accumulate in the cell and lend it the characteristic appearance of a spherocyte. Their diameter is less than that of normal red cells and they are rapidly destroyed in the spleen. The disease begins in childhood and is usually manifested by moderate anaemia. Haemolytic crises occur under the effect of unfavourable environmental conditions.

Fever and pain in the left hypochondrium caused by sharp enlargement of the spleen are encountered during the crises and soon after they cease. A remission occurs in a few days. The frequent crises cause the development of anaemia, jaundice and splenomegaly and pigment stones form in the gall bladder, which sometimes leads to attacks of cholelithiasis. Trophic ulcers on the shins and retardation of growth and mental development of the children is encountered in rare cases.

The diagnosis of congenital spherocytic (haemolitic) jaundice is based on the appearance of the red cells. They are smaller than the normal cells but are coloured more intensively. Their osmotic resistance is diminished. Clinical recovery occurs after splenectomy, though microspherocytosis remains. Coombs' test is always negative in this disease.

Congenital non-spherocytic haemolytic jaundice (anaemia). Research has shown that in the Soviet Union this disease is mostly encountered in the Azerbaijan SSR. It occurs in individuals whose red cells contain a deficient number of enzymes concerned with glycolysis. A deficiency of enzymes participating in the hexose cycle is found in some cases and a deficiency in those concerned with the pentose-phosphate cycle in others. G-6-PD deficiency is encountered particularly often in the inhabitants of Central Africa and somewhat less frequently among people living along the shores of

the Mediterranean Sea. The haemolytic process is triggered in them either by some acute infection or by some drugs, for instance, sulphonamides, furantoines (furfuran), anti-malarial agents, phenacetin, para-aminosalicylic acid, and phenylhydrazine.

Pain in the abdomen and small of the back, fever, anaemia and jaundice appear during haemolytic crises. In mild cases, jaundice appears only after the crises. In severe cases it becomes permanent. The spleen is always enlarged in permanent haemolysis. In congenital non-spherocytic haemolytic anaemia red cell morphology is normal. The diagnosis of the disease is made by testing the enzyme concentration in the red cells. Splenectomy is ineffective in this form of haemolytic anaemia.

Deficient activity of enzymes participating in the pentose-phosphate cycle (triosephosphate isomerase, pyruvate kinase) leads to graver haemolytic anaemia marked by permanent jaundice and splenomegaly. Only a single anomaly, moderate macrocytosis, is found in the stained blood smear of these patients. Its existence is explained by the predominance of younger forms among the red cells. The diagnosis of the disease may only be established after tests for the activity of the pentose-phosphate cycle enzymes.

Sickle-cell anaemia. The haemoglobin molecule consists of four haem molecules and four polypeptide chains. The replacement of the amino acids in the polypeptide chains results in the formation of abnormal haemoglobins.

Haemoglobin S is most common among the abnormal haemoglobins. Red blood cells containing this haemoglobin are distinguished from the normal cells by two features. Under conditions of hypoxia they acquire a shape resembling a sickle and show a tendency to formation of thrombi. Their life span is shorter than that of the normal red blood cells. The abnormal haemoglobin S is inherited. Haemolytic anaemia is encountered only in homozygotes. Heterozygotes do not suffer from anaemia. Sickle-cell anaemia is mostly encountered in Africa, the Middle East, and India.

The disease sets in in early childhood. It is clinically manifested by anaemia, fever, pain in the joints and muscles, thromboses of small vessels of different organs, and trophic ulcers of the lower limbs. The systolic murmur caused by anaemia and the arthralgia are often mistaken for the manifestation of rheumatic fever. The spleen is enlarged in children, but in adults it is reduced in size because of scarring of the numerous infarcts. Jaundice develops soon after crises. The diagnosis is based on the characteristic sickling of the red cells and the identification of haemoglobin S during electrophoresis.

Thalassaemia. Haemolytic anaemia and jaundice marked by a high content of iron in the serum are sometimes encountered in the Mediterranean countries. The disease is caused by congenital hae

moglobin deficiency. In a healthy person foetal haemoglobin disappears almost entirely from the blood a few months after birth. In patients with thalassaemia it persists throughout life. Most patients homozygous for this pathological condition die in childhood. Severe haemolytic anaemia (Cooley's anaemia) develops by the end of the first six months of life.

Heterozygous forms of thalassaemia (thalassaemia minor) usually develop without marked jaundice. Thalassaemia minor is often mistaken for other forms of anaemia.

The diagnostic signs of the disease are as follows: high resistance of red cells to hypotonic sodium chloride solution; high iron content in the serum; hypochromic anaemia; a characteristic (target-like) shape of the red cells. The content of foetal haemoglobin in the blood of these patients sometimes attains 20 per cent. Its content in a healthy person does not exceed 4 per cent. In other abnormal haemoglobins jaundice is extremely rare.

Paroxysmal nocturnal haemoglobinuria, or Marchiafava-Micheli disease, is an acquired malady. Crises in this disease are sometimes attended by mild jaundice. Haemoglobinuria is found in the morning because haemolytic crises develop at night in most cases. Abdominal pain and thromboses of small veins occur during the crises. The spleen is enlarged. Morphology of the red blood cells is normal.

Paroxysmal nocturnal haemoglobinuria should be suspected in all patients suffering from haemolytic or hypoplastic anaemia. The diagnosis should be verified by the demonstration of increased tendency of the patient's red cells to haemolysis when the serum is acidified (Hein's test).

Acquired (autoimmune) haemolytic anaemia may be acute or chronic. In about half the cases of anaemia of this type the cause remains unknown. The principal disease is recognized in approximately 40 per cent of cases. Most commonly it proves to be lymphogranulomatosis, lymphatic leukaemia, diffuse diseases of the connective tissue, ulcerative colitis, paroxysmal cold haemoglobinuria, and some infectious diseases, for instance, malaria, sepsis, toxoplasmosis.

As the name of the disease indicates, all these anaemias are characterized by the presence in the blood of an antibody capable of lysing the red cells. Removal of the causative factor in such cases does not lead to the cessation of haemolysis. Coombs' test is always positive. Certain diagnostic significance is attached to the favourable effect of corticosteroids on the course of anaemia.

All forms of jaundice occurring as a consequence of increased red cell breakdown present no considerable diagnostic difficulties. They are easily distinguished from jaundice developing in affections of the liver. Far more frequently they are misdiagnosed as various

anaemias, particularly if haemolysis is mild and there is no bright yellow pigmentation of the skin.

Hepatogenic Jaundice with Unconjugated Bilirubin

Bilirubin forms from haem and enters the blood bound with albumin. This form of bilirubin is insoluble in water. In the hepatic sinusoids bilirubin is transferred from blood plasma to the hepatocytes. In passing through the hepatocyte membrane bilirubin is freed from the albumin. On the way from the blood capillary to the bile capillary it binds with glucuronic acid. This reaction occurs on the hepatocyte microsomes and is catalysed by the enzyme glucuronyl transferase.

Any factor capable of disturbing the uptake of bilirubin by the hepatocyte or impairing its conjugation with glucuronic acid leads to the accumulation of unconjugated bilirubin in the blood. This bilirubin yields an indirect van der Bergh's reaction. It is insoluble in water and not detected in the urine. The accumulation of unconjugated bilirubin in the blood is an obligatory sign of congenital non-haemolytic forms of jaundice among which Gilbert's, Crigler-Najjar, Lucey-Driscoll syndromes and some other (acquired) forms are now distinguished.

Gilbert's syndrome. The accumulation of unconjugated bilirubin in the blood is most commonly manifested as Gilbert's syndrome described for the first time in 1901. This congenital non-haemolytic jaundice develops because the uptake of bilirubin on the vascular pole of the hepatocyte is impaired and because its transport to the microsomes of the hepatocyte endoplasmic reticulum is disturbed. Mild glucuronyl transferase deficiency is revealed in addition in some patients. The second variety of the disease is far graver than the first.

The disease prevails among females. Its first clinical manifestations usually appear in puberty. If the disease is manifested later in life, it must be differentiated from posthepatitic hyperbilirubinaemia. In the mildest cases of Gilbert's syndrome, the uptake and excretion of bromsulphthalein and Bengal rose by the hepatic cells are not impaired (Jio et/al., 1974).

The disease is inherited according to the autosome-dominant type and questioning of the patient about jaundice among his relatives may therefore provide a valuable clue to the malady. Examination of persons suffering from Gilbert's syndrome reveals moderate jaundice and the asthenic syndrome. The serum bilirubin content ranges from 0.02 to 0.04 g/l. Infection and physical or mental overstrain are attended by intensification of jaundice. The asthenic syndrome with its characteristic complaints of rapid fatigue and irritability

is noticeably augmented during an exacerbation of the disease. The liver and spleen are normal in size.

In considering the diagnosis of Gilbert's syndrome, it must be taken into account that these patients do not suffer from skin itching despite jaundice of long standing. Liver function is not changed, the urine contains no bilirubin and the prescription of corticosteroids does not lower the blood bilirubin concentration.

The content of indirect bilirubin in the blood of 3-4 per cent of patients with a history of virus hepatitis remains elevated six months to two or three years. This posthepatitic hyperbilirubinaemia is often mistaken for a recurrence of hepatitis; it is encountered more frequently among young males, is marked by periodical intensification and abatement of jaundice and always terminates favourably. Exacerbations of the disease are induced by physical and emotional overstrain and by alcohol. Incapacity of the hepatocytes to take up bilirubin from the blood and transport it to the microsomes underlies the syndrome.

In the posthepatitic syndrome, the liver is often slightly enlarged, but functions normally. Needle biopsy reveals neither signs of parenchymatous degeneration of the hepatic cells nor signs of inflammation in the stroma of the organ. Non-haemolytic jaundice with increased content of indirect bilirubin in the blood may be encountered after toxic hepatitis and after the prescription of male fern extract.

Familial non-haemolytic jaundice of the newborn (Crigler-Najjar syndrome) is an extremely rare disease. In this syndrome the concentration of indirect bilirubin in the blood increases because the process of its conjugation with glucuronic acid is disturbed. Two forms of the disease are distinguished. Total absence of glucuronil transferase is noted in the hepatic cells obtained by needle biopsy in some cases and marked diminution of the activity of this enzyme in others.

Jaundice appears soon after the child's birth, and gradually grows in intensity. In total absence of glucuronyl transferase the blood bilirubin concentration rapidly reaches a level of 0.2-0.4 g/l. The accumulation of bilirubin in the basal ganglia of the brain is attended by severe neurological symptoms. In this type of syndrome bilirubin does not enter the bile. Infants usually die before they are 12 months old.

Diminished glucuronyl transferase activity is transmitted as a recessive trait. Jaundice in these children is less severe. The cerebral nuclei are not involved. A small amount of bilirubin conjugates with glucuronic acid and enters the bile. No signs of haemolysis are found and all functional liver tests, the bromsulphthalein test among others, are normal.

Cases of severe familial non-haemolytic jaundice have been de-

scribed in which the serum of sick children inhibits glucuronyl transferase activity in the hepatic cells of healthy animals (the Lucey-Driscoll syndrome). Non-haemolytic jaundice of infants may be acquired. Cases of non-haemolytic jaundice of long standing developing in association with breast milk feeding have been described. The accumulation of indirect bilirubin in the blood was caused by the inhibition of glucuronyl transferase activity by 3α-20β-pregnanediol which was detected in the milk of the wetnurse.

A temporary increase in the concentration of unconjugated bilirubin in the blood is sometimes encountered after the intake of alcohol, in the use of contraceptive pills containing oestrogens, during menstruation, pregnancy as well as during treatment with agents excreted from hepatocytes by the same transport systems which excrete bilirubin. Among them are rifadin (rifampicin), morphine, and contrast media used in cholangiography and cholecystography.

Hepatogenic and non-hepatogenic forms of jaundice marked by accumulation of unconjugated bilirubin in the blood may be differentiated at the patient's bedside. A high reticulocyte count is always found in all non-hepatogenic forms. High reticulocytosis makes it possible to reliably rule out congenital and acquired non-haemolytic jaundice with the accumulation of indirect bilirubin in the blood. More or less marked haemolysis is attended by anaemia. The importance of this sign in making the diagnosis is obvious from the fact that the obsolete term 'haemolytic jaundice' has been replaced by 'haemolytic anaemia'.

Other signs easily detected at the patient's bedside are of no less diagnostic significance. Particular importance should be attached to the size of the spleen. In haemolytic jaundice it is enlarged, as a rule, whereas in congenital non-haemolytic jaundice it is always normal in size.

A sudden rise in body temperature in haemolytic anaemia is always attended by the appearance or noticeable intensification of pain in the abdomen, joints, and bones of the limbs or spinal column. Fever is followed by intensification of jaundice, increased reticulocytosis and the development of graver anaemia. Haemoglobinuria indicative of intravascular red cell haemolysis is sometimes encountered. The signs mentioned are not found in hepatogenic forms of jaundice marked by the accumulation of unconjugated bilirubin in the blood.

Jaundice with Conjugated Bilirubin

Conjugated bilirubin formed on the microsomes of the hepatic cell is excreted into the bile capillary from which it enters the duodenum. This process of transport may be impaired either within the

cells (along the distance from the microsomes to the bile capillaries) or outside the liver. In the first instance, bilirubin is retained in the hepatic cell and returns into the blood. Intrahepatic cholestasis develops which is now considered to be the principal cause of all hepatocellular forms of jaundice.

Hepatic and extrahepatic forms of jaundice with accumulation of conjugated bilirubin in the blood are commonly distinguished (see Supplement VIII-2). Extrahepatic jaundice is often designated 'obstructive' or 'surgical' jaundice. We included the Dubin-Johnson and Rotor's syndromes in the group of hepatogenic cholestatic jaundice, with which some authors might not agree.

Jaundice in lesions of the liver may occur acutely or develop gradually. It may be shortlived or longstanding. Proceeding from the tasks of differential diagnosis, we found it expedient to group all hepatogenic conjugated hyperbilirubinaemias into acute and chronic forms. Infectious or toxic acute hepatogenic jaundice may be distinguished depending on its cause. Chronic jaundice is usually induced by intrahepatic cholestasis.

Hepatogenic Jaundice with Conjugated Bilirubin

Acute infectious hepatitis is an extremely widespread disease. Twenty-eight different viruses have been isolated from the blood of patients with acute hepatitis. Coxsackie viruses (types A and B), echoviruses, adenoviruses, reoviruses, enteroviruses, mycoplasma, etc. are isolated particularly often. Infectious hepatitis (A virus hepatitis, hepatitis with a short incubation period) and serum hepatitis (B virus hepatitis, hepatitis with a long incubation period) are of major practical importance. Hepatitis with a short incubation period usually sets in acutely; hepatitis with a long incubation period often develops without jaundice.

Virus hepatitis is manifested morphologically by necrosis and autolysis of the hepatic cells in combination with leucocytic and histiocytic infiltration. The necrosis is most conspicuous in the centre of the lobules, while the cellular infiltration is most obvious in the portal tract. Hyperplasia of the epithelial cells with their focal clusters is sometimes encountered simultaneously. Proliferation of the biliary ducts is often seen. The clinical manifestations of the disease are very diverse and inconstant.

Virusaemia develops in the prodromal period and its severity varies from one case to another. Anorexia and nausea are the most common symptoms in this period. In practice they are encountered in every case of the disease. The prodromal (preicteric) stage of the disease lasts one or three days to four weeks. In most cases it lasts

three to five days. Fever develops in more than half the cases and disappears one or two days after jaundice develops.

The dyspeptic syndrome is often joined by pains in the epigastrium and right upper abdominal quadrant. Sometimes they are very intensive resembling the pain in hepatic colic. Pain in the throat, enlargement of the lymph nodes, diarrhoea and arthralgia appear at times. In this stage of the disease the hepatocyte membranes become permeable to intracellular enzymes which enter the blood. Increased activity of blood transaminases is the earliest sign of the disease. Hepatomegaly is often but not always found in this period of the disease.

In most patients the urine darkens at the end of the prodromal period and bile pigments appear in it. Enlargement of the liver is found in 25-90 per cent of cases of virus hepatitis in the icteric stage. Enlargement of the spleen is revealed in approximately a third to half the cases. The precipitation tests become positive by this time. It is our experience that the cephalin test is the most sensitive among them. The more commonly used sublimate test is far less sensitive. Leucopenia is found in the blood in uncomplicated cases and leucocytosis in those complicated by necroses.

Jaundice is sometimes the first and only clinical sign of the disease. After it appears, the patient's subjective condition noticeably improves. The dyspeptic syndrome disappears. Jaundice is first detected on the sclerae. The mucous membrane of the soft palate and under the tongue is stained later. The yellow colour of the sclerae, mucous membranes and skin is best detected in daylight.

The principal signs of this period of the disease are: hepatomegaly, pain crises 'caused by swelling of the liver' (E. M. Tareev), splenomegaly and bilirubinuria. Enlargement of the gall bladder, skin itching, and temporary absence of stercobilin are encountered in rare cases. The laboratory signs of the disease in the icteric period are very obvious. Increased activity of aldolase and transferases is particularly important in the differential diagnosis.

Massive necrosis of the liver (acute and subacute atrophy of the liver) usually occurs as a complication of virus hepatitis. It may also develop under the effect of hepatotoxic poisons of plant or industrial origin. Nausea, vomiting, and severe headache appear in a patient with extreme muscle weakness. Jaundice sharply intensifies and acquires an ochreous reddish tinge. The liver turns soft, sharply tender and begins shrinking. The spleen remains enlarged. A sweetish, nauseating mouth odour, the haemorrhagic syndrome, oedema of the subcutaneous tissue, and ascites appear. Body temperature is normal, though fever sometimes develops.

Azotaemia and oliguria appear in the terminal stage of the disease. Death occurs in approximately 75 per cent of cases of massive

necrosis of the liver, usually with the clinical picture of hepatic coma.

The duration of jaundice in virus hepatitis varies from a few days to several months; in about 10 per cent of cases the stool is completely discoloured. In some cases we were able to palpate a distended gall bladder. Skin itching often occurs and alkaline phosphatase activity increases. The clinical picture of the disease resembles that of jaundice associated with obstruction of the extrahepatic bile tract by a tumour or a stone. The true cause of the disease is easily established after tests for transferase activity and hepatic function.

The epidemic and serum forms of hepatitis are the most frequent but not the only cause of acutely developing jaundice. The jaundice syndrome is a component of the clinical picture of some forms of brucellosis. Jaundice is often encountered in acute lobar pneumonia, leptospirosis, amoebiasis, portal pylephlebitis, relapsing fever, herpes, and other diseases; the clinical picture of these diseases is so peculiar, however, that they are easily differentiated from virus hepatitis at the patient's bedside.

In the infectious hepatitis group special attention should be focused at **hepatitis** often developing **in infectious mononucleosis** (Filatov's disease). Clinically manifest jaundice is encountered in approximately 5 per cent of cases of this disease and is thought to be caused by simultaneous infection with Epstein-Barr virus. The febrile period of this disease is usually marked by hepatomegaly and splenomegaly. Severe tonsillitis with massive exudate on the tonsils, which is resistant to the usual therapeutic measures, is often found simultaneously.

The differential diagnosis of jaundice in infectious mononucleosis from jaundice in virus hepatitis is based on the detection of other signs of these diseases simultaneously with jaundice. In infectious mononucleosis fever continues after the appearance of jaundice; this never happens in virus hepatitis. Jaundice in infectious mononucleosis is encountered simultaneously with tonsillitis, lymphadenopathy, characteristic blood changes, positive Paul-Bunnell test, and typical recurrences of the disease. Simultaneous affection of many systems and organs may also occur in severe virus hepatitis. Differential diagnostic significance should be attached not only to the presence of these signs, but to their correlation with the severity of the general condition. Lymphadenopathy and splenomegaly in infectious mononucleosis may be very vividly manifest, whereas the patient's general condition is usually less severe than in virus hepatitis.

Toxic and drug-induced forms of hepatitis are grouped separately in pursuance, first and foremost, of coping with the practical task of their timely diagnosis and prevention. Some drugs (inhibitors

and monoaminoxidases, chloramphenicol, halothane, biomycin, terramycin, chlorpromazine hydrochloride, thiasine diuretics, para-aminosalicylic acid, cytotoxic agents, and other drugs) sometimes have a direct toxic effect on the liver. The resulting hepatitis hardly differs from virus hepatitis in the clinical manifestations and course.

The disease begins with a short prodromal period and a mild dyspeptic syndrome. Jaundice appears next. The liver is slightly enlarged and tender to palpation. Hyperbilirubinaemia and high transferase activity in the serum appear. The findings of needle biopsy are insufficient for differentiating this type of the disease from virus hepatitis.

In other instances, these agents cause an allergic affection of the liver. Jaundice in such cases is preceded by itching, urticaria, arthralgia, vasculitis, eosinophilia, and leucopenia. Hepatitis often occurs after the person takes negligibly small doses of the agent, for instance, after only one chlorpromazine hydrochloride tablet. As a rule, the disease follows a course similar to that of cholestatic hepatitis which is sometimes mistaken for obstructive (extrahepatogenic) jaundice.

Prolonged medication with androgens and anabolic steroids also induces cholestatic jaundice sometimes. The condition is distinguished morphologically from virus hepatitis by the absence of cellular infiltrates in the portal zone. Jaundice usually develops between the 10th and 15th days of treatment and at times one or two months after the drug has been discontinued. Jaundice is very intensive and attended by skin itching and discoloration of the stool. Its course is usually favourable, though protracted in some cases.

The differential diagnosis between toxic and virus hepatitis is based on the medical history. Questioning of the patient reveals that prior to the jaundice he had taken one of the drugs mentioned above. The occurrence of virus hepatitis is not associated with the intake of these agents. The precipitation liver tests and transferase activity are similar in these two diseases.

Virus hepatitis is sometimes attended by enlargement of the lymph nodes, leucopenia and early enlargement of the spleen. In drug induced toxic hepatitis the lymph nodes are not enlarged and the icteric period is marked, as a rule, by leucocytosis caused by more or less massive necrosis of the liver. Catarrh of the upper respiratory tract, diarrhoea and arthralgia are not encountered in drug induced hepatitis, but are quite a frequent occurrence in virus hepatitis.

Most mild forms of toxic hepatitis are marked by focal affection of the liver. The blood bilirubin content is normal or only slightly increased, while the alkaline phosphatase content is almost always above normal values. The discrepancy between these functional tests may be explained allowing that the functional reserve of the

liver as regards alkaline phosphatase excretion is much less than that with regard to bilirubin excretion.

Intrahepatic cholestasis. Approximately one third of patients suffering from acute virus hepatitis have cholestasis, a condition in which bile does not enter the duodenum despite the absence of a mechanical obstruction. In the first days of the disease, cholestasis is usually combined with the pain syndrome and must be distinguished from acute extrahepatic cholestasis. In about 10 per cent of cases virus hepatitis has the clinical picture of chronic cholestasis. Some authors believe it expedient to distinguish a cholestatic form of virus hepatitis which characteristically tends to take a protracted course.

The general condition of these patients is satisfactory, body temperature is normal, the precipitation liver tests are often negative, and the serum protein content does not change. A dark urine testifies to the excretion of conjugated bilirubin. Stercobilin is detected in traces, but sometimes it is not found at all for seven to ten days. This is particularly often encountered in elderly patients. A more or less intensive skin itching and usually a moderately increased blood alkaline phosphatase content consummate this clinical picture.

Moderate jaundice may persist two to six months. The precipitation liver tests are positive in the first two or three weeks of the disease, but negative later. Serum transferases are slightly increased. The light yellow or reddish tinged jaundice takes on a slaty hue later. The liver is slightly enlarged as a rule. The spleen is enlarged in about a third of cases.

In such cases needle biopsy reveals dilatation and proliferation of the biliary ducts, accumulation of bile in the bile capillaries, mild granular degeneration of the hepatocyte protoplasm, and inflammatory infiltration of the periportal regions. A greenish-brown liver is seen on laparoscopy. The disease follows a protracted course but recovery is complete in most cases.

The development of intrahepatic cholestasis is associated either with affection of the hepatocyte excretory function along the distance from the lysosomes to the bile ductule or with affection of the intralobular cholangioles under the effect of the virus or a chemical agent. Some authors attribute principal importance to compression of the bile capillaries by the periportal infiltrates.

The picture of intrahepatic cholestasis sometimes develops in exacerbation of chronic hepatitis and due to the effect of a variety of drugs. Some granulomatous diseases, e.g. sarcoidosis, are sometimes complicated by cholestatic hepatitis which responds well to corticosteroid therapy. The icteric period of cholestatic hepatitis which may last for up to 12 months is marked by moderately increased activity of blood alkaline phosphatase and cholesterolaemia

which sometimes leads to the development of xanthomas. In many cases jaundice is rapidly relieved by corticosteroids.

The cholestatic form of hepatitis sometimes develops in females in the last trimester of pregnancy. It is assumed that jaundice occurs only in females who are hypertensitive to an increased content of sex hormones in the body. It is characterized by persistent itching, absence of cyclic fluctuations in the level of bilirubinaemia, increased ESR, elevated blood cholesterol level, and slightly increased transferase activity. Jaundice disappears two weeks after pregnancy, on the average. A similar jaundice develops in these females after they take oestrogen containing contraceptives.

Acute cholestasis occurring at the onset of virus hepatitis and in exacerbation of chronic hepatitis in alcoholics is attended by pains and is often so severe that it must be distinguished from obstructive (extrahepatogenic) jaundice. The epigastric pain is evidently caused by stretching of the Glisson capsule. We were able to palpate an enlarged gall bladder in some of these patients. This was possibly due to concomitant involvement of the pancreas whose swollen head compressed the common bile duct.

We made note of the sudden appearance of pain in the right hypochondrium and enlargement of the gall bladder only in elderly and old patients. In such cases the diagnosis of virus hepatitis may only be made when association of the jaundice with obstruction of the bile duct by a stone or tumour has been ruled out.

Questioning the patient about the state of his health before the appearance of jaundice allowed vividly manifested symptoms and signs of the preicteric period of virus hepatitis (severe arthralgia, anorexia, fever, diarrhoea, etc.) to be revealed in some cases. Such signs never precede obstructive jaundice.

With the occurrence of jaundice in a patient with virus hepatitis fever disappears as a rule, the ESR is normal and the leucocyte count reduced. If the spleen is enlarged and the results of the functional liver tests (for blood aldolase and transferase content) are sharply abnormal, it is recommended to postpone intended surgery. In such cases abdominal pain disappears in one or two days, the gall bladder is no longer palpated, and the clinical picture of typical virus hepatitis develops.

Analysis of the signs mentioned above allows the diagnosis of virus hepatitis to be made in most cases without resorting to auxiliary examination. Rare cases of this disease are encountered, however, in which fever, the pain syndrome, and leucocytosis persist after the jaundice, while the content of aldolase and transferases is only moderately increased. Such combinations usually occur in alcoholic hepatitis, cholangitic hepatitis, and in obstruction of the bile duct with early development of concomitant cholangitis. Acholia may also be absent when the bile duct is only partly obstructed

by a stone, and the presence of weakly stained faeces cannot therefore be considered as evidence in favour of infectious hepatitis.

The difficulties of differential diagnosis in such cases can be overcome either by weighing the patient's condition for some time or by applying additional methods of examination. The condition of the patient, unfortunately, does not permit delaying decision for any length of time sometimes, and the internist is faced with the choice between retrograde cholangiography, needle biopsy of the liver, laparoscopy or laparotomy. The choice of the method depends on how well the hospital is equipped.

When any of these methods can be applied, it must be borne in mind that the differential diagnosis between cholangitic hepatitis and obstruction of the bile tract may be established with assurance only by means of laparotomy. It is far from every case in which the diagnosis is not clear that trial steroid therapy can be applied, because its results become evident only after a few days. Moreover, it is our experience that its results are often insufficiently convincing, and what is more, the use of steroid hormones in a case with suspected cholangitis seems to be insufficiently substantiated.

Primary biliary cirrhosis. Many facts have recently been accumulated which point to the autoimmune origin of this rare disease primarily due to affection of the bile ducts and portal tract draining the hepatic lobules. The clinical and biochemical picture of cholestasis clarifies in the late stages of the disease. It has been suggested that cholestatic hepatitis of virus, drug and granulomatous origin and primary biliary cirrhosis should be regarded as different manifestations of one and the same disease.

The disease may occur at any age, but most often it begins between 30 and 40. Females account for 90 per cent of all patients with primary biliary cirrhosis and xanthomatosis. The incidence of this disease with no concomitant xanthomatosis is the same among males and females.

The onset of the disease is insidious. According to some authors, skin itching is the first sign in most cases. It intensifies gradually and becomes intolerable. Patients apply to the dermatologist, but all local and general therapeutic measures are usually unsuccessful. Jaundice, the second principal sign of the disease, develops a few months, often a few years later. It may sometimes appear ten to twenty years after the itching begins. In some cases, skin itching and jaundice occur almost simultaneously. In about 2 per cent of cases jaundice precedes itching. There is absolutely no itching in 6 per cent of patients.

Sometimes skin itching occurs for the first time during pregnancy. The attendant jaundice in such instances is mistaken at first for cholestatic jaundice of the last trimester of pregnancy. As it was

noted above, cholestatic jaundice disappears soon after delivery. Skin itching and jaundice caused by primary biliary cirrhosis do not disappear after the infant's birth. The correct diagnosis in some cases of primary biliary cirrhosis may evidently be made after a more or less lengthy follow-up of the course of the disease.

In the first years of the disease, patients with primary biliary cirrhosis have the appearance of strong and healthy people with dark yellow skin. They are radically different from cachectic, pale patients suffering from portal cirrhosis of the liver. The skin of patients with primary biliary cirrhosis is thick, coarse, dry, and has traces of scratching. Depigmented areas at times alternate with hyperpigmented areas.

There is no pain in the region of the liver and body temperature is normal. In the initial period of the disease, the liver is slightly enlarged in most patients, but it may be normal in size or very large. Xanthelasmas sometimes appear when the blood bilirubin content is normal. Later, when hypercholesterolaemia is permanent, xanthomas develop first on the palms and the tendons of the elbow joints and then on the chest and buttocks. They usually disappear or diminish noticeably in the late period of the disease.

At the beginning of the disease, jaundice is moderate and the serum bilirubin content in 41 per cent of patients is below 0.02 g/l. A wavelike increase in bilirubinaemia is noted during the disease. In the terminal stage the serum bilirubin content may exceed 0.2 g/l. Splenomegaly is encountered in more than half the cases. Ascites, dilatation of the oesophageal veins, and hepatic insufficiency appear only in the terminal stage of the disease. The concentration of alkaline phosphatase rises at the onset and remains high or very high throughout the disease. Marked increase in the concentration of M immunoglobulins is a characteristic feature. The content of other immunoglobulins in the blood is normal.

Attention has been focused in the last decade at the accumulation of antibodies to the inner mitochondrial membrane in the blood of patients suffering from primary biliary cirrhosis. Antibodies against mitochondria are identified in 80 to 93 per cent of cases of primary biliary cirrhosis. Their titres correlate neither with the severity nor with the duration of the disease. Treatment with steroid hormones and immunosuppressants does not lead to the disappearance of these antibodies. Most authors consider it doubtful that these antibodies bear any differential diagnostic significance.

The diagnosis of primary biliary cirrhosis may be made in the early stages on the basis of pathognomonic changes in the morphological structure of the liver. These changes are particularly well demonstrated in biopsic material obtained during operation. The

following signs are considered to be characteristic of the disease: abnormal structure of the septal and interlobular bile ducts; infiltrates of lymphocytes, histiocytes, epithelial and plasma cells and a small number of eosinophils arranged around the bile ducts. Granulomas often form in these infiltrates. In all other respects the portal tract is normal. Small clusters of mononuclear cells may form in the lobules. Cholestasis is usually slight or not found at all.

Proliferation of the bile ducts and acute and chronic inflammatory infiltration develop in the later stages of the disease. Granulomas are a much less frequent occurrence. Necroses of hepatocytes are seen around the portal tract. After the inflammation ends, acellular connective tissue strands spread from the portal tract around the lobules. Cholestasis and deformity of the bile ducts are found. All these changes may be encountered both in primary biliary cirrhosis and in cirrhosis of other origin.

An initial (preicteric and icteric) and late (cirrhotic) stages may be distinguished in the course of primary biliary cirrhosis. Currently, the diagnosis of the disease in approximately half the cases is made in the preicteric stage and always before the picture of cirrhosis of the liver develops. The diagnosis of primary biliary cirrhosis is among the hard tasks. The disease must be first distinguished from obstructive jaundice (see below), constitutional jaundice with conjugated bilirubin (see below), lymphogranulomatosis of the liver, and from lupoid cholestatic hepatitis.

Primary biliary cirrhosis usually begins insidiously with an itch to which jaundice develops in attendance. Body temperature is normal. Virus hepatitis begins acutely after a more or less manifested prodromal period marked by fever, arthralgia and catarrhal phenomena. The blood alkaline phosphatase content in primary biliary cirrhosis increases long before jaundice appears, whereas in cholestatic hepatitis it is normal in the early period of the disease and slightly increases only some time after jaundice occurs.

The general condition of a patient with primary biliary cirrhosis is good for a considerable length of time after jaundice sets in. Only the excretory function of the liver is disturbed, which is demonstrated by increased activity of alkaline phosphatase in the blood and by hyperbilirubinaemia. Other liver functions (precipitation functional test, test for activity of transferases) do not change. Increased activity of aldolase and transferases is easily detected in the initial period of cholestatic hepatitis. Later their activity may diminish noticeably and only slightly exceed the upper normal limit. Before and immediately after the appearance of jaundice a patient with cholestatic hepatitis often complains of anorexia, pain in the region of the liver, and general weakness.

The above-described structure of the liver typical of primary biliary cirrhosis is never encountered in cholestatic hepatitis. In

the later stages of the disease, the morphological differences are less distinct. The results of trial therapy with prednisolone or its analogues may help greatly in the diagnosis in this period of the disease. Prednisolone administered for a week produces no noticeable effect on the course of primary biliary cirrhosis or on the severity of jaundice. Prednisolone therapy in cholestatic hepatitis is attended, as a rule, by marked decrease in the blood bilirubin level, diminution of transferase activity, and considerable improvement in the patient's general condition.

Constitutional jaundice (Rotor's and Dubin-Johnson syndromes). In 1954 Dubin and Johnson and, at the same time, Sprinz and Nelson described a new type of jaundice with conjugated bilirubin in the blood. The disease often sets in in puberty, although it may begin at any age. The disease is encountered in several generations of one and the same family. Its onset may be insidious or acute. In the latter case it is first mistaken for virus hepatitis.

Jaundice is of an intermittent character. The blood bilirubin content is usually no higher than 0.04-0.06 g/l. Exacerbations of jaundice occur under the effect of intercurrent infections and are manifested by general weakness and pain in the right hypochondrium. Jaundice practically disappears entirely during a remission. The liver is enlarged and rather firm in most cases. The spleen is palpated in about half the patients. The blood plasma protein content is normal. The activity of serum enzymes and the precipitation liver tests are normal. Bile pigments are detected in the urine. No signs of increased haemolysis are found.

Tests for bilirubin, bromsulphthalein and Bengal rose tolerance showed that impaired transport of bilirubin from the lysosomes to the bile canaliculus is the underlying factor of jaundice. In the clinic this abnormality is revealed during cholecystography. The contrast medium enters the bile very slowly and the gall bladder is therefore often weakly contrasted. Sometimes it is not demonstrated at all.

After intravenous infusion in a large dose (0.5 mg/kg) bromsulphthalein is rapidly taken up by the liver and remains in the hepatic cells for a long time. According to the results of scanning, radioactive bromsulphthalein is usually retained in the liver for ten hours, at times much longer. The normal rate of blood clearance from bromsulphthalein or some other dye is combined in the Dubin-Johnson syndrome with delayed excretion of the dye into the biliary tract.

This type of impaired excretory function of the liver is only encountered in the Dubin-Johnson syndrome. With its identification the diagnosis of this type of constitutional jaundice can be made without resorting to needle biopsy.

When the tests mentioned above cannot be carried out, the diagnosis may be established from the findings of needle biopsy of the liver. A greenish-brown pigment is found in the hepatic cells. The lobular structure of the liver is not impaired. During laparoscopy one can see that the liver is of a homogeneous dark green or black colour.

Familial jaundice described by Rotor is a consequence of the reduced capacity of the hepatic cells for bilirubin uptake, which is proved by the slow rate of blood clearance from the infused dye (Jio et al., 1974). Rotor's syndrome also differs from Dubin-Johnson's syndrome by the absence of greenish-brown pigment in the hepatic cells. The disease takes the course of protracted jaundice with a moderately increased concentration of conjugated bilirubin in the blood. Despite the long duration of jaundice, liver functions in patients with Rotor's syndrome are normal.

The differential diagnosis of Rotor's syndrome from Dubin-Johnson's syndrome is based on the findings of liver biopsy. The liver cells never contain a dark pigment in Rotor's syndrome. Moreover, in this syndrome the infused dye is noticeably retained in the blood but is excreted from the liver at a normal rate. X-ray examination shows a clearly contrasted gall bladder, which is explained by the absence of disturbances in the intracellular transport of bilirubin.

Constitutional jaundice of the type of Rotor's and Dubin-Johnson's syndromes is distinguished from primary biliary cirrhosis by less marked bilirubinaemia, no tendency to follow a progressive course, by a normal blood immunoglobulin content, the absence of itching, and an absolutely different histological structure of the liver. A long time elapses before jaundice leads to the development of cirrhosis of the liver in these syndromes.

Constitutional jaundice with conjugated bilirubin must sometimes be distinguished from virus hepatitis and primary carcinoma of the liver. Normal blood transferase activity and protein composition and a satisfactory general condition, notwithstanding the sudden onset of jaundice, make it possible to distinguish constitutional jaundice from virus hepatitis without conducting needle biopsy or any other invasive methods of examination. The differential diagnosis from primary carcinoma of the liver is discussed below.

Primary carcinoma of the liver. Jaundice occurs in more than half the patients with carcinoma of the liver. In some cases it develops in attendance to hepatomegaly, in others it appears at the beginning of the disease, usually simultaneously with dull, not very intensive pain in the region of the liver. The second variant is encountered much less frequently than the first. Jaundice developing in concomitance with hepatomegaly is not intensive, as a rule. Its occurrence in such instances is attributed to necroses of the he-

patic cells. It is a major, although not the principal sign of the disease. The bile tract in these patients is not obstructed, the stool is coloured, and bile pigments are found in the urine.

In recent years it has been suggested to distinguish a peculiar icteric variant of primary carcinoma of the liver. Obstructive jaundice closely resembling jaundice in cholelithiasis predominates in the clinical picture in such cases. Jaundice usually occurs after an attack of sharp abdominal pain attended by vomiting, fever and leucocytosis. The recurrence of such attacks imitates the clinical picture of cholelithiasis complicated by cholangitis. A wavelike intensification of jaundice is encountered in some cases. Obstruction of the bile ducts by necrotic masses or blood from a hepatoma that had ruptured into their lumen is found during operation or on autopsy in such cases.

A cholangioma-type primary carcinoma of the liver usually develops close to the hepatic porta. This leads to early compression of the bile ducts and early development of stable obstructive jaundice. There may be no pain or fever in this type of tumour. The liver is either moderately enlarged or normal in size. All other manifestations of cholangioma are like those of hepatoma.

Primary carcinoma of the liver may begin with various syndromes but marked weakness and rapid fatigue (the patient is 'drained of strength') appear soon after the onset of the disease in all cases, making the patient apply for medical advice. Hepatomegaly is among the most constant signs of the disease. The liver usually grows very rapidly extending both up and down. Its upper border sometimes reaches the fourth intercostal space, while the lower border extends down to the entrance into the true pelvis. The border of the liver is sharp and always hard as a stone. The spleen is enlarged in approximately half the patients. Cachexia, ascites, and anasarca develop in the later stages of the disease.

It is extremely difficult to make the diagnosis of the icteric form of hepatoma and cholangioma arising close to the hepatic porta. Jaundice in such cases is caused by involvement of the hepatic cells and more or less marked obstruction of the bile ducts. Increased alkaline phosphatase activity suggests that these disorders are linked with a lesion of the liver and obliges the physician to search for a tumour by testing the patient's serum for the content of alpha-foetoprotein. This test is positive in 90 per cent of cases in primary carcinoma of the liver.

The tumour is localized by means of isotope or echographic examination of the liver, intravenous and retrograde cholangiography. Hepatic arteriography and laparoscopy with biopsy of suspected hepatic areas render considerable assistance. Diagnostic laparotomy is nonetheless still the most authentic method.

It is not difficult to distinguish primary carcinoma of the liver from the Rotor and Dubin-Johnson syndromes and from primary biliary cirrhosis by the patient's appearance and condition. The skin of a patient with primary carcinoma of the liver is light yellow and is elastic for quite a long time. In primary biliary cirrhosis it is dark green. Bilirubinaemia is never as high in carcinoma of the liver as in primary biliary cirrhosis. The chest muscles are atrophied in primary carcinoma of the liver, while the abdomen is noticeably distended due to the growing liver and ascites. The patient's appearance is that of a doomed man who is suffering intolerably. Patients with primary biliary cirrhosis or constitutional jaundice of the Rotor or Dubin-Johnson type never create such an impression. These diseases also differ sharply in their clinical course.

The initial forms of primary carcinoma of the liver resemble subacute cirrhosis of the liver in some cases. The differential diagnosis between them can nonetheless be made without much effort. The characteristic signs of primary carcinoma of the liver are rapid growth of the organ in the anteroposterior direction with extension of its upper and lower borders. It is our experience that measurement of the anteroposterior dimension of the liver in such cases is of high differential diagnostic importance. Continuous though mild pain in the region of the liver is characteristic of carcinoma but not encountered in cirrhosis.

The clinical picture of cholangitis may develop in attendance to primary carcinoma of the liver, but not to cirrhosis of the liver. When these symptoms and signs are insufficiently manifest, laparoscopy or scanning of the liver may be performed. The results of these methods allow diffuse affection characteristic of cirrhosis to be differentiated from its focal affection in a tumour.

Extrahepatogenic (Obstructive) Jaundice

Obstruction of the bile ducts by a stone. Most cases of extrahepatogenic jaundice develop as a consequence of obstruction of the common bile duct by a stone entering it from the cystic or hepatic duct. The jaundice is of a secondary character developing as a complication of cholelithiasis, and in making the differential diagnosis attention should be focused at the detailed analysis of the concomitant pain and febrile syndromes rather than at the degree to which some of the signs of jaundice are manifested.

In most cases, jaundice develops after an attack of hepatic colic which occurs suddenly, as a rule, usually at night. Without ignoring the role of fatty foods and alcohol in provoking attacks we would like to emphasize that there is no obvious cause for the colic. The

pain arises suddenly and, growing rapidly in intensity, becomes unbearable within a few minutes. Repeated vomiting brings no relief. The patient moans and tosses in bed in the attempt to find a more comfortable position.

Maximum pain is felt in the region of the gall bladder and epigastrium and in the region of the right shoulder blade and right shoulder. Retrosternal pain is also often encountered. Pain in the left hypochondrium or girdle pain arises when the pancreas is involved in the process. Alternately intensifying and weakening, the pain may continue for several hours or one or two days. A large amount of light urine is sometimes discharged at the end of the attack.

Hepatic colic is almost always attended by fever the level of which is determined by the intensity of the inflammatory process in the bile ducts and the patient's reactivity. In short attacks, the fever may probably be of neuroreflex origin, but in attacks of long standing when the fever is attended by leucocytosis and increased ESR its association with infection of the biliary tract must be admitted.

Stones are usually found in the gall bladder. The attack of pain arises in most cases during migration of the stone along the cystic duct. As soon as the stone enters the common bile duct the attack ceases because this duct is wider than the cystic duct and the stone obstructs it only partly. The bile flows over the stone. The pain reappears when the stone reaches the narrow intramural segment of the duct. Obstruction is total when the stone is stuck in this part of the duct and jaundice persists till the stone makes its way into the duodenum.

Obstructive jaundice develops approximately 24 hours after the onset of hepatic colic. It usually lasts just a few days, though in some cases it may be of long standing. When the jaundice does not disappear and body temperature remains high this indicates that the common bile duct is most likely obstructed in the region of the major duodenal papilla. In such cases acute pain soon ceases and only dull pain is felt in the right hypochondrium and epigastrium. The stool is colourless and the urine dark. Skin itching and intermittent fever with a chill develop. Leucocytosis with a shift to the left and increased ESR are evidence of concomitant infection of the small bile ducts. The liver is slightly enlarged and tender in such cases. The gall bladder is usually inpalpable.

Jaundice in incomplete obstruction of the bile duct gradually grows while its intensity is inconstant. It is attended by a mild pain syndrome and moderate fever. Jaundice of a long duration is usually complicated by cholangitis manifested by fever with recurrent chills, leucocytosis, and increased ESR.

The clinical picture of hepatic colic with attendant cholangitis and jaundice is sometimes encountered in cholelithiasis when the

stones are located in the hepatic ducts. Intrahepatic localization of stones often occurs in patients suffering from clonorchiosis, schistosomiasis, nematosis and other parasitic diseases of the biliary tract. The colic is usually induced in such cases by obstruction of one of the hepatic ducts and is accompanied by enlargement of the corresponding hepatic lobe. Jaundice develops rarely in these diseases.

Cholelithiasis with stones in the hepatic ducts (localized within and outside the organ) is often encountered in the countries of South Asia and Africa. Males suffer from the disease much more frequently than females. In about 20 per cent of cases of this 'eastern-type' cholelithiasis, the gall bladder contains no stones.

Compression of the bile ducts from the outside. Carcinoma of the head of the pancreas. Jaundice in cholelithiasis is caused by obstruction of the bile ducts from the inside, whereas jaundice in diseases of the pancreas is, in distinction, a consequence of compression of the bile ducts from the outside. Jaundice is among the main signs of carcinoma of the head of the pancreas. In about a fourth of all cases it precedes all the other manifestations of this disease. In later stages of carcinoma of the pancreas, jaundice is encountered in more than 80 per cent of cases.

On the basis of rich statistical material, Shelagurov (1970) arrived at the conclusion that pain is the earliest symptom of carcinoma of the pancreas. In approximately 75 per cent of cases it is the first manifestation. The pain is felt in the upper abdomen and small of the back.

Jaundice develops gradually in most cases with no pain and soon acquires the features of the pure obstructive type. The urine turns dark and the stool colourless. The intensity of jaundice grows incessantly. The yellow pigmentation of the skin is gradually replaced by a dark-green colour. Itching appears. Body temperature sometimes rises to subfebrile levels; at times it does not rise every day, but two-three times a week. The patient loses weight noticeably in this period of the disease.

Bile pressure in all ducts proximal to the obstruction increases. This is attended by their regular distension and leads to enlargement of the liver and gall bladder. A gall bladder which had been normal prior to the onset of the disease becomes enlarged under the effect of increased bile pressure to such an extent that it becomes palpable. Courvoisier attached very high diagnostic value to this sign.

According to Courvoisier's law, an enlarged gall bladder in an icteric patient is evidence that jaundice is not associated with cholelithiasis. The clinical experience of 150 years confirms the justness of this law and shows the impossibility of its reverse interpretation. It was found that the absence of gall bladder enlargement does not rule out carcinoma of the head of the pancreas.

Uniformity in the distension of bile ducts and the sites of their constriction and dilatation are determined by cholangiography and cholecystography. The methods of intravenous and endoscopic cholangiography are both accessible and safe for use in the clinic for internal diseases. The latter method is gaining evermore popularity. High-quality cholangiograms are produced in 80 to 90 per cent of cases with it. In prescribing such an examination it should be taken into account that endoscopic cholangiography often leads to an exacerbation of cholangitis which develops 36 hours after the examination, on the average.

The head of the pancreas may be enlarged by the time jaundice appears, although more frequently its size is normal. Its dimensions are judged from the results of X-ray examination conducted under conditions of duodenal hypotension or from the size of its shadow on tomograms made after retroperitoneal administration of air or oxygen. The findings of pancreas scanning cannot, as yet, fully satisfy the clinician, because the method is insufficiently sensitive.

Liver function in carcinoma of the head of the pancreas like in other types of obstructive jaundice becomes abnormal only after a more or less lengthy period from the onset of the disease. A marked increase in the activity of aldolase and transferases soon after jaundice occurs is of high differential diagnostic importance.

Mild and usually short-term jaundice is sometimes encountered in acute pancreatitis. It is not a principal sign of the disease and rarely gives rise to diagnostic difficulties. Jaundice in chronic pancreatitis develops as a consequence of cicatricial stricture of the terminal segment of the common bile duct. A history of chronic pancreatitis and in some cases signs of calcification of the pancreas suggest that jaundice is associated with a disease of the pancreas. The absence or drastic decrease of pancreatic enzymes in the duodenal contents may be noticeable testimony in support of this possibility. The final diagnosis is usually only made during operation.

Other diseases. Obstructive jaundice resulting from *compression of the bile ducts by cicatricial tissue*, which develops after operations in the abdominal cavity, is a very rare occurrence. This complication is sometimes encountered in patients who had undergone cholecystectomy. Obstructive jaundice induced by compression of the bile ducts by enlarged lymph nodes in the hepatic porta is an even less frequent condition. The diagnosis of malignant tumour metastasis to this group of lymph nodes usually presents no great problem because the diagnosis of the principal disease in most cases is clear by that time.

A *hydatid cyst* located on the inferior surface of the liver or in the lesser omentum may compress the common bile duct or even

cause its total obstruction. The picture of obstructive jaundice will be the consequence of this. A hydatid cyst growing from the inferior surface of the liver in the direction of the abdominal cavity is often inaccessible to palpation. The true cause of jaundice in such cases begins coming to light after eosinophilia, urticaria or some other indirect signs of ecchinococcosis are detected. In view of this, purposeful examination is carried out: a radiograph is made for detecting calcified hepatic cysts and Casoni's skin test or the haemagglutination test is performed.

Among the extremely rare cases of obstructive jaundice are those developing due to involvement of the common bile duct in processes of inflammation and scarring of a duodenal diverticulum. Occasional cases have also been described in which the common bile duct was compressed by a tumour arising from the duodenum, by an aneurysm of the hepatic artery or by an enlarged lymph node in lymphogranulomatosis.

Diseases of the bile ducts. Tumours. The clinical picture of obstructive jaundice is one of the early signs of tumour of the bile ducts. Most of these tumours are malignant. The major duodenal papilla is involved most frequently. Next in diminishing frequency are tumours of the common bile duct and tumours of the hepatic ducts. These last are localized, as a rule, at the bifurcation of the common hepatic duct. Tumours of the intrahepatic bile ducts are extremely rare and are usually described in sections dealing with primary tumours of the liver.

Tumours of extrahepatic bile ducts resemble cicatricial tissue macroscopically. They are compactly arranged, as a rule, do not grow into the surrounding tissue and metastasis is late and rare. Cholangitis and hepatic insufficiency develop in the later stages of the disease. The tumour remains very small in size for a long time; this is why the patient usually dies not from carcinoma toxicosis, but from hepatic coma or intrahepatic abscesses.

Obstructive jaundice attended by severe itching predominates in the clinical picture of malignant and benign tumours of the bile ducts. In some cases the itching precedes jaundice by one or two months. Intermittent jaundice is considered to be characteristic of tumour of the major duodenal papilla. In tumours of the bile ducts of other localization jaundice is always permanent. Rapid intensification of jaundice is extremely characteristic of bile duct tumour. One or two weeks after jaundice appears, the blood bilirubin content increases to a level of about 0.1 g/l. Rapidly developing weakness and marked loss of body weight soon after the appearance of jaundice are also typical.

The liver is enlarged early, but it is rarely tender. The gall bladder cannot be palpated when the tumour is located in the bifurcation of the common hepatic duct, but it may be enlarged

when the new growth is distal to the junction of the bile and cystic ducts.

The findings of cholangiography are determined by the localization of the tumour. When the tumour is in the bifurcation of the hepatic duct, the gall bladder is not demonstrated by means of intravenous cholangiography. In endoscopic cholangiography the gall bladder and extrahepatic bile ducts are filled normally in such cases. The intrahepatic ducts cannot be filled.

Endoscopy with the use of a fibroscope provides for examination of the duodenal mucosa and detection of a tumour of the major duodenal papilla. Retrograde cholangiography is not possible in such cases because the common bile duct cannot be entered. If the tumour is proximal to the site of the duct drainage, its position can be determined by endoscopic cholangiography prior to operation. Nonetheless, even now the exact topical diagnosis of the tumour is established only during operation in most cases.

Cholangitis is a regular complication of tumours of the bile ducts. Its development at the onset of the disease may be judged only from the increase in the leucocyte count and ESR. In the later stages of the disease a chill appears and a picture of purulent cholangitis develops which may lead to an unfavourable outcome of the disease.

Cholangitis. Inflammation of the bile ducts (cholangitis) is among the rather frequent causes of jaundice, especially in females. In most cases it develops in attendance to other diseases of the liver and gastro-intestinal tract and aggravates their course noticeably. *Escherichia coli* is the main parasite of the biliary tract, but in no less than a fourth of cholangitis cases the disease is caused by other microbes.

Bile stasis is believed to be the main factor predisposing to the development of cholangitis. The regular combination of cholangitis with lambliasis, opisthorchiasis, schistosomiasis, and other parasitic diseases gives grounds to many authors for considering these diseases to be important causes of inflammation of the biliary ducts.

The most common causes of bile stasis are tumours of the bile tract and pancreas, congenital and acquired stenoses of the biliary tract, total or partial obstruction of the bile ducts by stones or parasites, and their compression by tumours of adjoining organs, e.g. by enlarged lymph nodes.

Acute and chronic forms of cholangitis are distinguished. The findings of target liver biopsy show that the inflammatory process in the early stages of the disease involves not only the wall of the bile ducts (which are drastically dilated) but the adjoining periportal areas in which infiltrates of plasma cells, leucocytes and lymphocytes appear. Connective tissue forms in the periportal areas in the later stages.

Jaundice is not an obligatory sign of cholangitis. It is found in no more than one third of cases of this disease and always only in the late stages. In some instances it develops against the background of an acute febrile disease which is usually diagnosed as acute cholecystocholangitis. The fever may be continuous or intermittent. A recurrent chill occurs in the day and is followed by profuse sweating. Sepsis is at first suspected when continuous fever is combined with high leucocytosis (up to $15 \cdot 10^3$-$20 \cdot 10^3$ per 1 μl) and increased ESR. Cholangitis attended by intermittent fever but with no leucocytosis had been previously mistaken for malaria.

By the time that jaundice appears in a patient with cholangitis, pain in the right hypochondrium and hepatomegaly are always revealed and splenomegaly is also often found. Pain in the region of the liver is usually continuous and moderate. Sometimes it is replaced by acute pain of the type of hepatic colic. Jaundice in cholangitis is a consequence of obstruction to the flow of bile and not of affection of the hepatic cells. Excretion of alkaline phosphatase is simultaneously impaired. Increased activity of this enzyme is an important diagnostic sign of cholangitis.

The results of other excretory functional liver tests with bromsulphthalein, isorubin I or Bengal rose do not possess any high diagnostic significance. Positive results (like an increased blood bilirubin content) are evidence of obstructed bile flow and do not allow the functional condition of the hepatocytes to be appraised separately. Intravenous cholangiography often proves to be unsuccessful.

The chronic forms of cholangitis are either consequent upon acute cholangitis or occur as a primary disease. Diffuse affection of the bile ducts may lead to the development of secondary biliary cirrhosis of the liver although some authors deny such a possibility.

In most cases segmental cholangitis follows the course of a chronic disease with remissions replacing exacerbations. A stenosing lesion of the terminal segment of the common bile duct (sphincter of Oddi and the major duodenal papilla) is most common. Stenoses of the hepatic duct and its branches and stenoses of the common bile duct sometimes prove to be congenital, but most frequently they are a consequence of cicatricial changes in the bile ducts after surgery.

Jaundice in such cases is also a late sign of the disease. It develops as a rule in attendance to a long-existing dyspeptic syndrome. The liver is always enlarged by the time that jaundice appears. The spleen is also enlarged in many cases. The differential white blood count is usually normal, but the ESR is often moderately increased. Many cell components, leucocytes among others, are found in the bile (fraction C). Body temperature often remains at a subfebrile level for a long time. Most patients experience pain in

the region of the liver, which is usually moderate and replaced from time to time by attacks of acute pain of the type of biliary colic.

The association of jaundice with cholangitis seems very probable if, in studying the medical history, it is revealed that the patient had previously undergone surgery on the bile tract or that he had long been suffering from diseases commonly marked by impaired flow of bile from the liver (namely, carcinoma of the pancreas, calculous cholecystitis with attacks of hepatic colic and obstructive jaundice in the past, recurrent episodes of acute pain in the region of the liver with vomiting and more or less prolonged period of elevated body temperature attended by jaundice).

One may confidently speak of the connection of jaundice with cholangitis if hepatomegaly and splenomegaly appear during the disease and a large number of leucocytes and cells of the biliary epithelium are found in the bile (fraction C). The final diagnosis of stenosing cholangitis may only be made from the findings of cholangiography. Dilatation of the bile ducts proximal to the site of the stenosis is considered a characteristic sign.

Supplement XVII-1

Causes and Types of Jaundice

I. Jaundice with unconjugated bilirubin.
   1. Non-hepatogenic.
      Congenital spherocytic haemolytic anaemia (jaundice).
      Congenital non-spherocytic haemolytic anaemia (jaundice).
      Sickle-cell anaemia.
      Thalassaemia.
      Paroxysmal nocturnal haemoglobinuria.
      Acquired (autoimmune) anaemias.
   2. Hepatogenic.
      Gilbert's syndrome.
      Familial non-haemolytic jaundice.
      Lucey-Driscoll syndrome.
      Other non-haemolytic forms of jaundice.

II. Jaundice with conjugated bilirubin.
   1. Hepatogenic.
      Acute virus hepatitis.
      Acute bacterial and other forms of hepatitis.
      Toxic and drug-induced hepatitis.
      Intrahepatic cholestasis.
      Exacerbation of chronic hepatitis.
      Jaundice in pregnancy.
      Primary biliary cirrhosis.
      Constitutional jaundice.
         Dubin-Johnson's syndrome.
         Rotor's syndrome.
      Primary carcinoma of the liver.

2. Extrahepatogenic (obstructive) jaundice.
   Compression of the bile duct from the outside.
      Carcinoma of the pancreas.
      Acute pancreatitis.
      Chronic pancreatitis.
      Ecchinococcosis (hydatid disease) of the liver.
      Duodenal diverticulum.
   Duodenal tumour.
   Aneurysm of the hepatic artery.
   Lymphogranulomatosis.
Diseases of the bile ducts.
   Tumour of the bile ducts.
   Cicatricial stenosis of the common bile duct.
   Cholangitis (acute, chronic, segmental).
Cholelithiasis.

Chapter XVIII

Oedema

Ever since Claude Bernard's time two environments of human existence have been distinguished, external and internal. The latter consists of fluids (fluid body components) whose volume, composition, and location are among the physiological constants of the body. Fluid accounts for approximately three fifths of human body mass. About 70 per cent of it is contained in cells, and about 30 per cent is extracellular. There exists a perpetual exchange of electrolytes and metabolites (amino acids, vitamins, fatty acids, carbohydrates, proteins) between the intra- and extracellular fluids.

The extracellular fluid consists of blood plasma which transports metabolites to the sites of their consumption and excretion and the fluid contained in the intercellular spaces. This interstitial fluid is a blood plasma transudate. Through it the products of metabolism enter the cells from the blood and are transported from the cells to the excretory organs.

Excessive accumulation of fluid in the interstitial space results in the development of oedema. Generalized and localized forms of oedema are commonly distinguished. The former develop in diseases of the heart, kidneys, liver and gastro-intestinal tract, the latter in diseases of the veins and lymphatics and in allergic inflammation.

The fluid in generalized oedema is distributed in accordance with the laws of gravity. In patients with heart failure who are in an orthostatic or semirecumbent position oedema first appears in the lower limbs and the lumbosacral region. If the patient can easily assume a recumbent position, oedema first appears in the face and hands, as one can easily see in children suffering from acute glomerulonephritis.

The accumulation of fluid in the body is explained by its diminished excretion by the kidneys. This excretion is regulated by intrarenal and extrarenal factors. The production and distribution of interstitial fluid may also be disturbed under the effect of mechanisms which are mainly active at the capillary level. The dependence of oedema formation on the height of the venous pressure is easily seen in patients with mitral stenosis and left-ventricular failure in whom oedema primarily occurs in pulmonary circulation.

The hydrostatic blood pressure is not the same in all organs. For example, average blood pressure in the pulmonary capillaries ordinarily does not exceed 10 mm Hg, whereas blood pressure in the

capillaries of the renal glomerulus is about 75 mm Hg. Even in one and the same organ, e.g. in the lower limbs, capillary pressure changes sharply, depending on a person's position. The average capillary pressure in the foot of a person of middle height rises to 110 mm Hg in a standing posture. This also explains the appearance of pitting of the feet towards evening in persons who had worked all day in a vertical posture. Puffiness under the eyes in the morning is attributed to the combined effect of very low intratissue pressure in these regions with temporary increase of capillary pressure due to the person's recumbent position throughout the night.

Oedema also forms when the colloidal osmotic pressure of blood plasma drops below 20 mm Hg. Since this pressure is mainly produced by albumins their reduced content in the blood is often attended by oedema included in the group of hypoproteinaemic oedema (Supplement XVIII-1).

The content of proteins in blood plasma may drop as a consequence of either decelerated rate of their synthesis or increased loss from the body. The rate of synthesis of albumins and some globulin classes is determined by the functional condition of the liver. The blood plasma protein content also depends on the diet. Lack of proteins in the diet is the main cause of hypoproteinaemia in alimentary dystrophy and kwashiorkor. Hypoproteinaemia is one of the consequences of the malabsorption syndrome often developing in diseases of the gastro-intestinal tract. Loss of protein in the urine, stool, vomitus and ascitic and pleural fluid also leads to hypoproteinaemia.

Mucopolysaccharide deposits in the skin and subcutaneous tissue of the distal segments of the upper and lower limbs in myxoedema are sometimes mistaken for manifestations of heart failure. The skin on the dorsal surface of the hands and feet of a patient with myxoedema is not thinned out as in heart failure, but rough and thick. There is no pitting on pressure. Pitting may occur from light pressure applied to the skin only in simultaneous existence of myxoedema and heart failure. The diagnosis of myxoedema is confirmed in such cases by the existence of its other signs and the results of trial thyroidin therapy. The prescription of thyroidin in myxoedema is attended by moderate diuresis. The detection of oedema is no clue either to its origin or to the prognosis or methods of treatment. It is relatively easy to make the diagnosis in cases of localized oedema. The cause of its origin can be recognized in most cases by means of clinical methods of examination. The mechanisms of the formation of generalized oedema are insufficiently known and cannot be used as grounds for making the differential diagnosis. The system of the differential diagnosis of oedema given below is based on the identification of its traditional association with diseases of the cardiovascular system, kidneys, liver, and gastro-intestinal tract.

Oedema develops in these diseases under the effect of several simultaneously existing mechanisms. Proper appraisal of the role of the principal mechanism is of decisive importance for the prognosis and method of treatment.

The internist most frequently deals with oedema caused by diseases of the heart which in the Soviet literature are designated by the term grade IIB or III heart failure. Much less frequently the physician has to deal with oedema whose underlying factor is affection of the kidneys (the nephrotic syndrome) and liver. Oedema developing in diseases of the gastro-intestinal tract has attracted more and more attention in recent years. Hypoproteinaemia is the most constant sign of this oedema; it is always encountered in oedema in a patient whose diet lacks protein.

Oedema Occurring Mainly under the Effect of Local Factors

Dilatation of the arterioles and precapillary sphincters as well as increased venous pressure are capable of noticeably increasing fluid transudation through the capillary wall. Oedema in such cases is evidently caused not only by increased capillary pressure, but by increased permeability of the capillary wall to blood plasma components. Clinical experience shows that increased capillary pressure is only one of the conditions necessary for the formation of localized oedema. Disorders of the trophic function of the sympathetic nervous system is evidently among the additional conditions. It is the effect of precisely this factor that explains the absence of oedema in aortic insufficiency and its invariable occurrence in polyneuritis and also in cases when patients are treated for a long time with ganglion-blocking agents and agents which block the endings of the sympathetic nerves, e.g. ismelin. The same origin may evidently be true of oedema of the involved limb in a patient with hemiplegia and summer oedema in the region of the malleoli often appearing in females in hot weather. There is no room for doubt that this factor is important in the development of oedema of the brain and optic papilla in severe arterial hypertension. The more widespread opinion concerning the ischaemic origin of this oedema cannot explain why there is no oedema in ischaemia of other organs and tissues.

Increased pressure in the venous limb of the capillary in combination with reduced pressure in the tissue surrounding the capillary are probably extremely important causes of the formation of postural oedema of the lower limbs in persons whose jobs keep them on

their feet for a long time without considerable muscular exertion. The same factors play an important role in the development of oedema in limbs the venous drainage of which is blocked by a tumour, scar or by thrombosis of the draining vein. There is no doubt that the same factor contributes significantly to the formation of oedema of the limb in varicosities. It may be that these factors are responsible for the development of oedema in convalescents when they are put on their feet the first days after a long period of absolute bedrest.

Lymphatic Oedema

The internist is often faced with patients who have asymmetric oedema in the lower limbs. These are usually young females who had been unsuccessfully trying to relieve oedema by means of various combinations of cardiac agents for many years. In most cases this oedema proves to be lymphatic.

Two types of lymphatic oedema are distinguished: primary (congenital) oedema consequent upon a congenital developmental defect of the lymph vessels of the lower limbs and secondary (acquired) oedema developing in inflammation of these vessels. Lymphatic oedema in patients with filariasis and other parasitic diseases of the lymph vessels is not encountered in the Soviet Union because the sources of infection have been totally eradicated. Lymphatic oedema occurring in obstruction of the lymph vessels by a tumour is not within the limits of the internist's practice.

Primary non-inflammatory lymphatic oedema of the lower limbs is called congenital when it appears for the first time in childhood, early, when it occurs between the ages of 10 and 20, and late when it is manifested for the first time after the age of 30. This last variant of the disease is most common. Only one lower limb is at first involved, and usually moderately. Oedema in both limbs develops later but one limb is swollen more than the other, as a rule.

Inspection and palpation usually reveal a clear boundary between the oedematous and non-oedematous part of the limb. At the beginning of the disease oedema is found only up to the level of the ankle. In later stages it spreads up to the knees and in far-advanced stages, as far as Poupart's ligaments. In the early stages of this disease, oedema may sometimes vanish for several years. Oedema is at first soft, but it gradually gains firmness after recurrent lymphangitis and cellulitis. The limbs become disfigured only after long years of the disease. Not only the lower, but the upper limbs are also involved in rare cases.

In his practice the internist often encounters lymphatic oedema of the upper limb of females who had undergone radical operation

for mammary carcinoma. The diagnosis of this type of lymphatic oedema usually causes no difficulty.

Premenstrual Syndrome and Oedema in Pregnancy

Oedema in the region of the malleoli is often found in the late period of normal pregnancy. Late toxaemia of pregnancy is attended by considerable oedema developing under the effect of increased capillary pressure, diminished plasma colloidal osmotic pressure, and retention of water and electrolytes by the kidneys. Water and electrolytes are retained during pregnancy because there is an excess of oestrogens and progesterone in the body of the expectant mother. Their disappearance is attended by puerperal diuresis. The proof of this hypothesis lies in the fact that the loss of sodium in the urine in the puerperal period can be prevented by prescribing large doses of oestrogens and progesterone.

Oedema associated with the menstrual cycle is evidently also of hormonal origin. One often encounters females with anasarca in whom even thorough examination reveals no signs of a disease of the heart, kidneys or liver. The premenstrual syndrome is diagnosed in many of them after a long follow-up period. These females usually become irritable, emotionally unbalanced, and easily tearful for no obvious reason in the second half of the menstrual cycle. They often suffer from weakness and headaches. Disturbed sleep (insomnia or hypersomnia) is a particularly characteristic sign. Increased appetite, pigmentation of the face, and attacks of hypoglycaemia are also typical features.

Signs indicative of fluid retention in the body are at first mild. Slight oedema appears in the malleolar region in the premenstrual period, particularly if the woman is kept standing on her job for long periods of time (by the end of work her shoes feel too tight). The breasts sometimes swell. Swelling of the gums makes the dentures uncomfortable. Some patients have pains in the joints and muscles. Oedema is more marked in hot than in cold weather. In some cases fluid retention is not attended by clear clinical symptoms and is revealed because of growth in body weight.

Sometimes these patients have attacks of migraine and epilepsy in the premenstrual period, possibly as a consequence of localized oedema of the brain. Dizziness experienced from time to time may also be considered a manifestation of oedema of the structures of the internal ear.

The diagnosis of the premenstrual syndrome may be regarded

sufficiently substantiated if the above-described symptoms occur regularly every month. Intensifying gradually in the second phase of the cycle they become especially marked on the eve of menstruation. After menstruation ceases, the patient's condition improves and signs of fluid retention disappear or diminish noticeably.

Opinions about the incidence of the premenstrual syndrome are very controversial. This is probably due to the different amount of attention accorded to the symptoms described above, both by physicians and the patients themselves.

The exact aetiology of the premenstrual syndrome is not known. The commonly accepted hypothesis of its association with disturbed hormonal function of the ovaries cannot explain all the facts accumulated in the clinic to date. It is still not clear, for instance, why signs of the premenstrual syndrome (oedema among others) persist even after menstruation ceases. Deficient ovarian hormonal function is evidently only one of its causes.

The diagnosis of the premenstrual tension syndrome may only be made after long-term observation of the patient and after all other causes of water and electrolyte retention in the body are ruled out.

The cyclic character of the disorders of water-electrolyte metabolism and the coincidence of the period of maximum fluid retention with the premenstrual days are the main clinical signs of this syndrome. Heart failure must usually be ruled out in cases difficult from the standpoint of diagnosis. This is most reliably accomplished by measuring blood pressure in the right atrium and the venae cavae.

Nephrotic Syndrome

The nephrotic syndrome is a complex of signs developing in increased permeability mainly of the renal glomeruli to blood plasma proteins. In the clinic the diagnosis of the nephrotic syndrome is based on the combination of marked proteinuria with hypoproteinaemia and oedema. Hyperlipidaemia and lipuria are also often revealed.

The nephrotic syndrome is now considered to be one of the developmental stages of many renal diseases. Biopsy of the kidney is recommended for establishing a maximum precise aetiological diagnosis in each case of this syndrome. The results of such examination are particularly essential for planning the therapeutic tactics and judging the prognosis with regard to survival and recovery.

Patients with the nephrotic syndrome usually complain of somnolence and rapid fatiguability which probably occur under the effect of a negative nitrogen balance and frequently encountered

anaemia. Some patients complain of anorexia and diarrhoea which may partly be attributed to oedema of the gastro-intestinal mucosa; in addition to oedema many patients complain of numbness of the limbs and a foamy urine.

Oedema in the nephrotic syndrome is always generalized. It is only evident when the patient's body mass increases by 10 to 15 kg. At the onset of the disease nephrotic oedema is mostly found in areas with low intratissue pressure in the periorbital region, in the genitals, small of the back, anterior abdominal wall, and the feet. The distribution of oedema in the late stages of the disease is governed by the law of gravity. Oedema in the conjunctiva and sclera is often attended by deterioration of vision, particularly in children. In some cases, oedema develops gradually, in others rapidly within 24 hours. Ascites, hydrothorax, and hydropericardium appear at the peak of the nephrotic syndrome. In oedema of a long duration, the skin is pale, dry and atrophic, and striae of distension (striae atrophica) form on it. Now these striae are usually associated with prolonged corticosteroid therapy.

Accelerated protein breakdown leads to marked muscle atrophy which is particularly conspicuous when oedema subsides. Treatment with corticosteroids usually contributes to still greater atrophy of musculi quadratus femoris. Arterial pressure is normal in most patients or even tends to decrease. During corticosteroid therapy it sometimes rises. High hypertension is a poor prognostic sign in children it is sometimes attended by hypertensive encephalopathy.

In the nephrotic syndrome the fluid may seep through the fissures in the skin to its surface. Pneumococcal peritonitis and infectious diseases of the skin and lungs were the most frequent complications of the syndrome in the past. In our times, bacterial infections have no decisive effect on the course of the disease. It seems to us that this may be explained by the possibility of avoiding persistent oedema rather than by the wide use of antibiotics. The same fact explains the sharp decrease in the incidence of nephrotic crises manifested by abdominal pain, repeated vomiting and diarrhoea.

High significance is attributed to laboratory data in the diagnosis of the nephrotic syndrome. A healthy person excretes about 20 mg of protein in the urine daily. This negligible amount of protein cannot be detected by the routine laboratory methods. Daily excretion of protein in the nephrotic syndrome with normal rate of glomerular filtration usually varies from 5 to 20 g. Higher values are encountered in rare cases. Excretion of protein in the urine in one and the same person varies sharply in different days.

Two forms of proteinuria are distinguished in the nephrotic syndrome. In some cases the amount of protein that had passed through

the glomerular filtre considerably exceeds the reabsorption capacity of the tubular part of the nephron. This mechanism of proteinuria has been proved in animal experiments. It could have been unconditionally applied also to human pathology if it had been proved that in the nephrotic syndrome the urine proteins cannot be secreted by the cells of the tubular epithelium. In other cases of the nephrotic syndrome, the glomerular membrane is impermeable to normal serum proteins but is easily permeable to abnormal proteins, for instance, Bence Jones protein.

The theory of the selectivity index is the practical application of the above-stated conceptions. Corticosteroids are often effective in the nephrotic syndrome with selective proteinuria and rarely effective in non-selective proteinuria.

Hypoproteinaemia is among the constant signs of the nephrotic syndrome. There is a particularly sharp fall in the blood albumin content. The globulin concentration is normal or even slightly increased. In cases of non-selective proteinuria it may also be normal. Considerable loss of protein in the urine and stool is attended by its accelerated synthesis, but the total content of protein in the body decreases noticeably because processes of catabolism prevail. The serum protein content is determined not only by the rate of protein synthesis and breakdown, but also by its dilution in the oedematous fluid.

Loss of albumin in the urine and stool is believed to be the initial link in disorders of protein and water-electrolyte metabolism in the nephrotic syndrome. Oedema appears when the blood albumin content falls to 25 g/l. Sodium excretion sometimes ceases completely in the period of oedema formation. Other renal functions are often normal. In some cases of the nephrotic syndrome creatinine clearance rises to 200 ml/min. This fact is commonly explained by secretion of creatinine by the tubules and not by intensified glomerular function. When creatinine clearance falls below 10 ml/min, massive proteinuria usually ceases and oedema disappears.

The milk-white tinge of blood serum in the nephrotic syndrome is attributed to the increased content of lipids in it. Hypercholesterolaemia is a particularly characteristic sign. It has been noted that the content of cholesterol in the blood changes in inverse relationship to the content of albumin in it. Following intravenous infusion of albumin, the blood cholesterol content decreases temporarily. No such distinct inverse connection has been found between the concentration of albumin and triglycerides in the blood.

Hypoalbuminaemia inevitably leads to a decrease in the plasma oncotic pressure as the result of which the plasma volume reduces by 20-30 per cent, on the average. In severe affection of the kidneys, massive proteinuria may reduce drastically the content of intravascular protein, the consequence of which is severe hypovolaemia.

It usually develops acutely and is often the cause of collapse.

The urine of patients with the nephrotic syndrome possesses high relative density. Its sediment contains hyaline, granular, epithelial and wax casts, leucocytes, doubly refractile lipids and fatty-degenerated cells of the tubular epithelium. The content of red blood cells in the sediment is determined by the character of the main disease. They are often found in the urine of patients with chronic nephritis and systemic lupus erythematosus and much less frequently in those with amyloidosis and Crohn's disease.

The **causes of the nephrotic syndrome.** Some variants of the nephrotic syndrome differ in the clinical picture, course and character of the morphological changes in the kidneys. The most common causes of the syndrome are listed in Supplement XVIII-2. Besides them, there are many other factors capable of inducing a kidney affection marked by the development of the nephrotic syndrome. The generally accepted clinical and laboratory methods of examination often cannot yield sufficient information for solving very important problems of diagnosis, treatment and prognosis. It is therefore very natural for the physician to supplement the clinical and laboratory characteristics of the disease with morphological data.

It is precisely the findings of kidney biopsy that helped to establish that in approximately 80 per cent of cases the nephrotic syndrome is a developmental phase of glomerulonephritis. Among the other causes, which account for 20 per cent of cases of the nephrotic syndrome, the most frequent are metabolic diseases (diabetes mellitus, amyloidosis) and circulatory disorders in the kidneys induced by increased blood pressure in the renal veins or their thrombosis. The true frequency of the other causes of the nephrotic syndrome cannot be established because the data on them are received from specialized clinics treating patients suffering from specific diseases.

Glomerulonephritis

The term 'glomerulonephritis' is used to designate many kidney diseases. The clinical manifestations of these diseases are very diverse. In some cases they set in with acute encephalopathy, in others with the irreparable renal insufficiency syndrome. For many years they may only be manifested by moderate proteinuria or haematuria.

Since there is no aetiological classification, renal diseases are diagnosed descriptively. The descriptive classification is based either on the clinical syndromes (malignant, latent, terminal nephritis, etc.) or on the features of the histological structure of the kidney (proliferative, membranous-proliferative nephritis, etc.).

Acute and chronic clinical entities of nephritis are generally

distinguished. Acute nephritis is usually manifested by haematuria, proteinuria and hypertension. In rare cases it begins with the nephrotic syndrome. No histological changes may be detected in the kidney after clinical recovery. The clinical manifestations of chronic nephritis are very diverse. Histologically it is distinguished as proliferative (diffuse and focal) or membranous-proliferative nephritis, membranous nephropathy, and renal lesions with changes undetectable by light microscopy and at times undetectable on an electronogram probably because of the focal character of the lesion.

Strictly speaking, these two last types of affection may be only conditionally included in the group of inflammatory diseases of the kidneys. Occurring as a primary disease (i.e. in no association with any systemic diseases) they are always marked by the clinical picture of the nephrotic syndrome described above. Tareev describes these forms of renal lesions together and designates them conditionally using the terms 'membranous glomerulonephritis' and 'glomerulonephritis with minimum changes'.

Glomerulonephritis with minimum changes is predominantly encountered among children. It is registered in 10-20 per cent of adults suffering from the nephrotic syndrome. Its aetiology is not known. In some cases oedema and the entire clinical picture of the syndrome recur after contact with specific pollen and plant allergens. Arterial pressure is almost normal while proteinuria is always highly selective. The association of selective proteinuria and nephritis marked by minimum changes is so close that it is recommended to make its diagnosis in children even without needle biopsy.

Haematuria in the nephrotic syndrome with this form of the pathological condition is never massive. The degree of oliguria differs. In rare cases it is so sharp that dialysis must be conducted. The disease is marked by regular alternation of recurrences and remissions. The frequency of the recurrences decreases with time.

The nephrotic syndrome in membranous nephropathy (nephritis) and membranous-proliferative nephritis differs from the syndrome described above in that there is non-selective proteinuria and a graver course. Oedema may persist for several years. Sudden intensification of proteinuria is often the first sign of thrombosis of the renal veins. Slow progress of membranous nephritis is considered a characteristic feature. Its onset is usually insidious. Renal insufficiency may develop only in 20 years. The course of membranous-proliferative nephritis is less favourable. Death occurs from renal insufficiency in about five to seven years after the onset of the disease.

The nephrotic syndrome is sometimes the first manifestation of focal (lobular) nephritis which is encountered either as an independent isolated disease or as a manifestation of systemic dis-

eases of the connective tissue. Focal nephritis may also be manifested by isolated proteinuria appearing during an acute respiratory disease and lasting only one or just a few days. Recurrent haematuria is often observed.

Focal nephritis must sometimes be differentiated from acute poststreptococcal nephritis. When taking the medical history it is important to identify the time when oedema began. In focal nephritis it develops during acute respiratory infection whereas in poststreptococcal nephritis it appears 10 to 14 days after the disease ends.

Diffuse Diseases of the Connective Tissue

The nephrotic syndrome is often encountered in diffuse diseases of the connective tissue, particularly in systemic lupus erythematosus. Lupus nephritis is among the severest complications of the disease. According to the findings of kidney biopsy, it may be stated that the spread of the process to the kidney is at first manifested by focal glomerulonephritis which is no different from other forms of focal nephritis. Fibrinoid necrosis develops later in the foci of affection. The well known 'wire loop' is merely a localized thickening of the capillary loop. The picture of membranous nephritis is encountered very rarely. Sclerosis of the glomeruli, atrophy of the tubules, and infiltration of the interstitial tissue with inflammatory cell elements develop with time. The formation of a secondary contracted kidney is the end result of this inflammatory process which is extremely pleomorphic from the histological standpoint.

The nephrotic syndrome may be the first and even the only manifestation of systemic lupus erythematosus. In most cases, however, it develops when lupus nephritis already exists. According to Nasonova (1972), the nephrotic syndrome develops six months to seven years after the onset of the disease, usually during one of its exacerbations. In the fifties the nephrotic syndrome was considered to be a rare complication of lupus erythematosus. Now it is encountered much more frequently. Tareeva found it in 30 per cent of patients. It is encountered particularly frequently among young females.

In most cases, oedema develops quite abruptly and quickly increases. Marked proteinuria and a great loss of protein with the stools lead to hypoproteinaemia and hypoalbuminaemia. The cholesterol content is often normal. Proteinuria in lupus nephritis complicated by the nephrotic syndrome is of a non-selective character as a rule. Both finely dispersed blood protein fractions (albumins, ceruloplasmin, transferrin) and coarsely dispersed blood protein

fractions (alpha-2-macroglobulin, gamma globulins) are excreted in the urine.

Lupus nephritis complicated by the nephrotic syndrome often resembles the subacute form of chronic nephritis in the clinical course with the characteristically rapid development of concomitant arterial hypertension and early development of renal insufficiency. Despite considerable loss of gamma globulins in the urine, their content in the blood remains increased. The prognosis of the nephrotic syndrome in lupus nephritis is always poor.

The diagnosis of the nephrotic syndrome is especially difficult when it is the first clinical manifestation of systemic lupus erythematosus. Many authors contend that the results of kidney biopsy in such cases have no diagnostic importance because lupus nephritis has no specific histological signs.

In the chronic form of systemic lupus erythematosus, the nephrotic syndrome usually develops during one of the exacerbations five to seven years after the onset of the disease. The extrarenal signs of systemic lupus erythematosus are sufficiently obvious by this time and it is therefore much easier to identify the cause of the syndrome. In rare cases, the nephrotic syndrome of lupus nephritis may be the beginning of subacute systemic lupus erythematosus. The disease usually attacks young females. The urinary syndrome remains after spontaneous disappearance of oedema and together with the usually slightly elevated arterial pressure imitates the clinical picture of chronic nephritis. The lupus origin of this nephritis is suspected when arthralgia, pleurisy, myocarditis, hepatomegaly and splenomegaly appear six to twelve months after the onset of the disease. When there are no extrarenal manifestations of systemic lupus erythematosus, the lupus nature of nephritis should be suspected if anaemia, leucopenia and drastically increased ESR occur in a young female suffering from nephritis. A clinical picture comprising many syndromes develops in the late stages of the disease in all patients with lupus nephritis.

The content of gamma globulins in the blood and urine is increased in lupus nephritis, while the blood gamma globulin content is noticeably below normal level in the classical type of the nephrotic syndrome. Hypercholesterolaemia is characteristic of the nephrotic phase of chronic nephritis; in lupus nephritis complicated by the nephrotic syndrome the blood cholesterol content is often normal. Drug intolerance is characteristic of most of these patients. Lupus cells are identified in the blood during an exacerbation and sometimes during a remission.

The results of needle biopsy of the kidneys are not of decisive importance themselves, but nonetheless may help considerably in detecting the cause of the nephrotic syndrome. Though the 'wire loops' and haematoxilin bodies are encountered in other connective-tissue

diseases, their identification in combination with the clinical and laboratory signs described above are evidence in favour of the diagnosis of lupus nephritis.

Glomerulonephritis is encountered in approximately 7 per cent of cases of rheumatic fever. The nephrotic syndrome only develops in severe forms of the disease, usually at the peak of one of its attacks. It is characterized clinically by marked proteinuria and hypoproteinaemia. The blood cholesterol content is slightly increased or normal. Oedema may be very considerable, but its origin should be linked not only with rheumatic fever and hypoproteinaemia, but with heart failure.

The daily loss of proteins in the urine in heart failure usually does not exceed 1 to 2 g. As soon as heart failure is compensated, protein loss in the urine sharply diminishes at first, and then no longer takes place. It increases markedly when heart failure is complicated by affection of the kidneys. Severely manifested oedema, hypoalbuminaemia, and ascites persist even after the haemodynamic signs of heart failure are corrected, i.e. after the size of the liver diminishes, venous pressure decreases, and blood stasis in the lungs is markedly relieved.

Glomerulonephritis in rheumatoid arthritis is commonly of the membranous or the membranous-proliferative type. According to Tareev (1972), glomerulonephritis predominantly occurs in turbulent development of the rheumatoid disease in young individuals. It usually occurs during an attack of the disease and follows a progressive course. It is difficult to distinguish its clinical manifestations from those of amyloidosis often encountered in this disease.

Glomerulonephritis attended by the nephrotic syndrome is encountered in a few cases in scleroderma. It cannot be ruled out that some of these cases of nephritis are possibly associated with the effect of drugs which patients are often obliged to take for a considerable time. The nephrotic syndrome appears not at the onset but only in far-advanced cases of scleroderma, dermatomyositis and rheumatoid arthritis. This makes the identification of its cause much easier.

Systemic Vasculitis

The nephrotic syndrome was diagnosed in 14.5 per cent of cases of haemorrhagic vasculitis and systemic affections of the capillaries and arterioles whose origin has not been exactly identified. The disease often occurs after a streptococcal infection or after exposure of the body to cooling, insulation or vaccination, and also after medication with certain drugs. Deposits of immunoglobulins, fibrin and complement in the glomeruli are evidence in favour of the activity of immune mechanisms of this disease.

Haemorrhagic vasculitis is attended by affection of the skin, joints, gastro-intestinal tract and kidneys. Other organs are rarely involved. The disease prevails among children and adolescents. Affection of the kidneys is diagnosed in almost 75 per cent of cases. It is usually benign. Adults have the disease less frequently but the renal lesion has no clear tendency to spontaneous healing. Involvement of the kidneys in haemorrhagic vasculitis has the character of focal nephritis in most cases. Diffuse lesions are much rarer. Like other forms of proliferative extracapillary glomerulonephritis, they are characterized by a subacute course.

The clinical picture of haemorrhagic vasculitis is comprised of the cutaneo-articular and abdominal syndromes and affection of the kidneys. The skin manifestations of the disease are always clearly manifest at young age. These are punctate eruption (exudative erythema), papules, and petechia which sometimes coalesce. There is often no skin manifestations in elderly patients. The articular syndrome is usually displayed as polyarthritis which is of a migrating character. Large joints are involved as a rule, which become enlarged because of periarticular swelling. Effusion into the articular cavity develops in rare cases.

The abdominal syndrome comprises episodes of abdominal pain, recurrent vomiting, gastro-intestinal bleeding or diarrhoea. Affection of the small vessels of the small intestine with haemorrhages into the mucous membrane and parietal peritoneum and oedema of the intestinal wall underlie this syndrome. The picture of acute abdomen develops occasionally. The abdominal syndrome is usually vividly manifest in children and adolescents. It may not appear at all in adults.

Involvement of the kidneys is usually found later than the skin, articular and gastro-intestinal manifestations of the disease or simultaneously with them. In rare cases, affection of the kidneys develops after the cutaneo-articular and abdominal syndromes had been fully revealed. Involvement of the kidneys in the process may be manifested by isolated proteinuria and the acute nephritis syndrome with oedema and hypertension.

The nephrotic syndrome may develop both in the acute period of the disease simultaneously with purpura, abdominal pain, vomiting, diarrhoea and pain in the joints and in the period of convalescence. Oedema first appears on the face and is soon joined by anasarca and accumulation of fluid in the cavities. Hypoproteinaemia and hypercholesterolaemia are found in the blood. Protein loss in the urine may be very considerable. Arterial pressure is either normal or elevated. Massive proteinuria, oedema and haematuria disappear in a few weeks or months. Recurrences of the nephrotic syndrome and its development into nephritis with a chronic course sometimes occur.

There is no difficulty in making the diagnosis of the nephrotic syndrome in haemorrhagic vasculitis if it develops in the acute period of the disease. It is far more difficult to identify its cause in the period of convalescence or when the skin lesions and signs of involvement of the small intestine are not sufficiently expressed. As it is pointed out above, this form of renal involvement is often observed in haemorrhagic vasculitis of adults.

Chronic nephritis in haemorrhagic vasculitis must be distinguished from the common post-streptococcal glomerulonephritis and from affection of the kidneys in systemic lupus erythematosus, periarteritis nodosa, rheumatic fever, and metabolic diseases.

The nephrotic syndrome in glomerulonephritis with minimum changes differs from this syndrome in haemorrhagic vasculitis by the presence of highly selective proteinuria, hyperlipidaemia, normal arterial pressure and the absence of attendant cutaneo-articular manifestations of the disease. This last factor is of no small significance in making the differential diagnosis at the sick child's bedside. The medical history is very important, although it is not always reliable. That is why, in all cases presenting some difficulty, renal biopsy may help in differentiating these forms of chronic nephritis.

The nephrotic syndrome in systemic lupus erythematosus differs from this syndrome in haemorrhagic vasculitis in that it takes a graver course. The differential diagnosis may be made with all assurance only if all extrarenal manifestations of these diseases are taken into consideration. Systemic lupus erythematosus is characterized by the presence of many syndromes, but this never happens in haemorrhagic vasculitis. The results of needle biopsy acquire differential diagnostic significance only when they are compared with the findings of biochemical examination and when the period of the clinical course of these two diseases is taken into account.

Affection of the kidneys is found in approximately 75 per cent of patients with periarteritis nodosa. In some cases lesions of the arcuate vessels with thrombosis and obliteration are found. Small infarcts form in areas supplied by them. In other cases the glomeruli are involved and the process takes the type of chronic glomerulonephritis (proliferative or membranous), sometimes with fibrinoid necrosis of the capillary loops.

The nephrotic syndrome is very rare in periarteritis nodosa and has no specific signs. It is manifested by great protein loss in the urine and hypoproteinaemia. The blood cholesterol level is normal or moderately increased. Oedema is far less intense than in the nephrotic syndrome of other aetiology. The combination of rapidly progressive nephrotic syndrome with extremely high arterial hypertension and neuroretinopathy is considered a characteristic feature. Haematuria is particularly conspicuous in cases with marked

hypertension. In most cases of this disease, affection of the kidneys occurs in a patient with long-term fever, arterial hypertension and severe abdominal pain. Other signs of periarteritis nodosa (loss of body weight, polyneuritis, vascular pneumonia) are of valuable assistance in making the diagnosis. The diagnosis is based on the combination of the extrarenal signs of the disease listed above with the urinary syndrome and arterial hypertension.

Infectious Diseases

According to different authors, the kidneys are involved in the morbid process in half or even in all cases of bacterial endocarditis. The developing clinical pictures are sometimes attributed to embolism of the renal artery, usually by colonies of bacteria vegetating on the affected area of the endocardium or vascular endothelium. This type of affection is manifested by haematuria and pain in the small of the back. A similar clinical picture develops in focal 'embolic' nephritis.

In recent years, bacterial endocarditis is becoming complicated more and more often by diffuse glomerulonephritis, which sometimes tends to progress rapidly. The infection can be managed in most cases by the modern methods of antibacterial therapy. Affection of the heart may be very mild in such cases and the patient's fate is determined by the course taken by glomerulonephritis.

The nephrotic syndrome is sometimes the first and most striking syndrome of bacterial endocarditis. In typical cases, mild transient oedema occurs in a patient with persistent subfebrile temperature and indisposition. True nephrotic oedema develops after some time elapses. It usually forms acutely on the face, shins and small of the back. A large loss of protein in the urine and reduced blood protein content occur simultaneously with oedema and in many cases moderate hypercholesterolaemia and increased ESR.

The general manifestations of the principal disease, bacterial endocarditis, change markedly under the effect of glomerulonephritis. Body temperature falls to a subfebrile level or in some cases remains normal. Arterial pressure is normal or only moderately elevated. The diagnosis of chronic nephritis is often made in such cases and only the development of a clinical picture of a formed heart valvular disease, or the appearance of splenomegaly and characteristic embolisms makes it possible to establish the correct but unfortunately delayed diagnosis of bacterial endocarditis.

In most cases, the nephrotic syndrome occurs not at the onset of bacterial endocarditis, but after the valvular disease has formed. Oedema occurring in this case is often mistaken for a manifestation of heart failure. Dysproteinaemia in such cases is often interpreted

as a sign of the principal disease. The development of concomitant nephritis comes to mind only after long-term treatment with cardiac glycosides and diuretics proves ineffective, or when attention is drawn to the extraordinary persistence of the urinary syndrome or to the development of hypostenuria.

The nephrotic syndrome is sometimes encountered in malaria, pyelonephritis and many other diseases. The mechanisms of its development in malaria have been studied in greater detail. It is found particularly often in children. Malarial nephritis may be focal or diffuse. The nephrotic phase of this nephritis is characterized by non-selective proteinuria and low sensitivity to cyclophosphamide, azathioprin and corticosteroids. It is fairly easy to make the diagnosis of the nephrotic syndrome in infectious diseases because it is a well known complication.

Amyloidosis

Increased loss of blood plasma proteins in the urine and stools leads to dysproteinaemia and eventually to hypoproteinaemia which, if sufficiently severe, is complicated by the nephrotic syndrome. Dysproteinaemia and hypoproteinaemia are often found in combination with amyloidosis of the kidneys which comes second in frequency after glomerulonephritis as the cause of the nephrotic syndrome.

Secondary Amyloidosis

Primary, secondary, and familial amyloidosis is generally distinguished. In primary amyloidosis, amyloid is prevalently deposited in the heart, gastro-intestinal tract, tongue, and spleen. The kidneys are involved in the process in 10 to 30 per cent of cases. Proteinuria is usually mild and does not lead to the development of hypoproteinaemia. The nephrotic syndrome is usually encountered in cases with secondary (acquired) amyloidosis developing in attendance to chronic infectious diseases, malignant tumours, and diffuse diseases of the connective tissue. In such cases amyloid is mainly deposited in the liver, spleen, kidneys, adrenals, intestine, and in the intima of vessels with a small and moderate calibre. Much less frequently the nephrotic syndrome is found in familial (hereditary) amyloidosis.

Amyloid deposits in the kidneys lead, before all else, to proteinuria, which may be moderate or marked, but first it appears only during exacerbations of the main disease. It disappears during remission. With time and the gradual accumulation of amyloid in

the glomeruli, proteinuria becomes stable and severer. In distinction from proteinuria in chronic nephritis, proteinuria in amyloidosis of the kidneys persists even when chronic renal insufficiency develops.

For the most part, albumins are lost in the urine at the onset of the process, proteinuria becomes non-selective later. Daily protein excretion in the urine may reach 20 to 30 g. 'Nephrotic crises' marked by a drastic increase in the loss of protein in the urine often occur under the effect of injury, infection and other states of stress. In concomitant amyloidosis of the intestine, we always observed the development of the syndrome of increased protein loss in the gastro-intestinal tract.

The loss of great amounts of protein in the urine and stools leads to hypoproteinaemia which is usually combined with dysproteinaemia. An increased content of gamma globulins and cholesterol in the blood is believed to be a characteristic feature. Hypercholesterolaemia often persists even when chronic renal insufficiency develops. Oedema forms in about half the cases of secondary amyloidosis, always in marked hypoproteinaemia.

In most cases of amyloidosis, arterial pressure is normal in the proteinuric and nephrotic stages of the disease. With the development of renal insufficiency it moderately increases in 10 to 20 per cent of cases. Hypertension crises are very rare. Red blood cells, leucocytes and hyaline, granular and wax casts are often found in the urinary sediment. Macrohaematuria is not frequently encountered and may be of non-renal origin.

Biopsy of the kidneys may yield direct proof of renal amyloidosis. Closed biopsy is usually performed. Amyloid is found in most glomeruli in the nephrotic stage of the disease. It is lodged under the epithelium of the capillary loops (often obstructing them noticeably), in the walls of the afferent arterioles, and in the mesangium of the glomerular vascular pole. Amyloid may also be found in other organs: the rectum, liver, and gums. Biopsy of these organs may confirm the diagnosis of amyloidosis, but kidney biopsy is nevertheless preferable. Examination of material obtained from the kidney may not only verify the presence of amyloidosis of this organ but establish the diagnosis of diseases which had not even been suspected and which would require adequate corrections to be made in the planned therapy.

Rheumatoid arthritis and tuberculosis are now the most common causes of amyloidosis of the kidneys whose rate of development differs noticeably from one case of another. Besides amyloidosis and glomerulonephritis, which are characteristically complicated by the nephrotic syndrome, pyelonephritis and interstitial nephritis sometimes develop in a patient with rheumatoid arthritis given analgetics and preparations of heavy metals for a long time.

The therapeutic methods used in treating these complications differ noticeably. The diagnosis of rheumatoid amyloidosis cannot be made reliably from the results of ordinary clinical and laboratory examinations, and the desire of the physician to make an exact morphological diagnosis in each case is only natural, for it is also necessary in choosing the most effective methods in managing the principal disease. The character of the lesion of the kidney is determined most authentically from the results of its biopsy.

Amyloidosis complicated by the nephrotic syndrome most frequently must be differentiated from the nephrotic phase of chronic glomerulonephritis. The medical history is particularly valuable in the differential diagnosis of these diseases. Amyloidosis is usually a second disease developing in attendance to diffuse diseases of the connective tissue, chronic infection or chronic suppuration. The first clinical signs of amyloidosis develop insidiously, whereas in the case of acute or chronic nephritis most patients can exactly identify when they became sick and describe the character taken by the disease as it develops.

The nephrotic syndrome in amyloidosis develops after a more or less lengthy period of proteinuria. Oedema forms first on the feet and shins. Ultimately it spreads to the thighs, small of the back, and genitals. If bedrest is prescribed in this period, oedema disappears but with the patient's return to physical activity it reappears like oedema in heart diseases. Anasarca and collection of fluid in the cavities may develop abruptly after injury, infection or after unidentified abdominal pain. Thrombosis of renal vein branches usually induces rather acute intensification of oedema.

Oedema develops acutely at the onset of nephritis, often at the same time as an attack of paroxysmal dyspnoea, elevation of arterial pressure, and encephalopathy. Acute development of oedema is also observed in exacerbation of chronic nephritis. Headache appears simultaneously with oedema in such cases. Arterial pressure may rise considerably. Haematuria noticeably intensifies during exacerbation but in chronic nephritis it never assumes the character of macrohaematuria. The latter is typical of amyloidosis and malignant hypertensive disease.

With the gradual development of azotaemia, oedema in chronic glomerulonephritis slowly diminishes and the patient is dehydrated. The development of uraemia in amyloidosis is only attended by a decrease in oedema and total dehydration of the patient does not occur. The blood cholesterol content is high. Enlargement of the liver and spleen is sometimes determined after oedema decreases in amyloidosis. The results of needle biopsy of the kidney are of decisive importance.

Familial Amyloidosis

In Tareev's clinical school, Vinogradova and Nasonova conducted detailed research into a hereditary metabolic disease encountered among young people of Jewish, Arab and Armenian descent. In some cases it is manifested by attacks of fever of a fixed pattern which cease without treatment and recur after various lapses of time. Sharp pain in the abdomen and chest occur simultaneously with the fever in most patients and polyarthritis develops. Due to this stereotype repeated character the disease was named periodic.

Both the patient and the physician involuntarily focus their attention at the vivid clinical manifestations of the disease while the metabolic disorders develop insidiously, ultimately leading to the development of amyloidosis. The fate of most patients is determined by the development of precisely this process. In some cases amyloidosis unnoticeably joins a disease of more or less lengthy duration, in others it develops simultaneously. Some authors described patients with isolated amyloidosis and patients with amyloidosis developing before the other clinical signs of the periodic disease.

Kidney amyloidosis in the periodical disease occurs as intermittent proteinuria which eventually becomes permanent. With the gradual increase in protein loss in the urine, hypoproteinaemia and concomitant oedema develop. When the nephrotic syndrome appears, the development of amyloidosis in the kidneys is noticeably accelerated. The disease transforms into the stage of chronic renal insufficiency. The duration of the proteinuric stage of the disease ranges from 12 months to 18 years, and the duration of the uraemic stage from two months to five years.

Hypoproteinaemia, hypercholesterolaemia and proteinuria are included in the clinical picture of the nephrotic syndrome in periodical disease. Macrohaematuria may occur both during the attacks of fever and independently of them. The appearance of macrohaematuria is always evidence of amyloidosis the timely diagnosis of which in essence determines the life prognosis.

When the nephrotic syndrome develops after a period of proteinuria in a patient with typical manifestations of the periodical disease, its cause is obvious. Proteinuria and the nephrotic syndrome may precede the other signs of the disease. Careful study of the familial medical history in combination with the findings of kidney needle biopsy helps in identifying the true cause of the malady in such cases.

The nephrotic syndrome sometimes also develops in other hereditary diseases, for instance, in the Muckle-Wells syndrome which

is also characterized by attacks of fever, recurrent urticaria, and progressive deafness. Kidney amyloidosis in this disease is manifested by proteinuria, which may lead to the development of the nephrotic syndrome and death from uraemia.

Another familial disease is the congenital nephrotic syndrome whose signs appear immediately after birth or within the first weeks of life. It terminates in death by the end of the first year of life. The nephrotic syndrome is also encountered in older children. Besides genetic factors, it may be caused by infectious, toxic and other factors.

Malignant Tumours

The nephrotic syndrome may develop in malignant tumours. It is a particularly constant occurrence in multiple myeloma which is characterized by osteolysis, hyper-, dys- and paraproteinaemia, i.e. the presence in the blood plasma of abnormal proteins produced by the plasma cells. Multiple myeloma is often attended by pathological conditions of the kidneys of various genesis.

Hypercalcaemic nephropathy in multiple myeloma develops under the effect of the excessive loading of the nephrons with calcium salts released during osteolysis. Such affections of the kidneys are also encountered in other malignant tumours marked by metastasis to the bones.

'Excretion nephrosis' develops due to total or partial obstruction of the distal tubules with casts of myeloma paraproteins. Tubular segments distal to the casts are dilated. Syncitium forms around the casts and the nephrotic syndrome is a clinical equivalent of this type of myeloma nephropathy.

In 5 to 10 per cent of cases multiple myeloma is complicated by kidney amyloidosis which, when quite severe, leads to the development of the nephrotic syndrome. Besides, urate nephropathy and pyelonephritis are often encountered in multiple myeloma.

The nephrotic syndrome in myeloma nephropathy usually develops after a protracted period of proteinuria. Up to 5 to 20 g of protein is lost in the urine daily. Paraproteins are found in the urine just as in blood. Bence-John's protein is a particularly frequent finding. The urinary sediment contains red and white blood cells and various types of casts among which giant casts of laminated structure are considered to be particularly characteristic. Hyperproteinaemia and dysproteinaemia are usually detected in the blood. The nephrotic syndrome in multiple myeloma is marked by mild oedema. Moderate azotaemia was found in all our cases.

Proteinuria and the nephrotic syndrome may be the first clinical signs of multiple myeloma which is usually mistaken for chronic

nephritis in such cases. Erythrocyturia, leucocyturia, increased ESR and anaemia may be found in both diseases. In making the differential diagnosis between them, special attention should be concentrated on the patient's age, the protein composition of the serum, and the results of X-ray examination of the bones and needle biopsy of the bone marrow and kidneys.

Multiple myeloma sets in only at elderly age, as a rule. The young age of the patient is unusual in this disease, but it does not contradict the diagnosis of chronic nephritis. Information on a history of acute nephritis is obtained, although far from always, only by questioning patients with chronic nephritis.

These two diseases differ noticeably in the serum protein composition. This is particularly distinctly seen in comparing the electrophoregrams. Paraproteins are identified only in the blood of patients with multiple myeloma which is also characterized by a marked increase in alpha-2, beta and gamma globulins and a high total blood protein content. Hypoproteinaemia is among the most characteristic signs of the nephrotic syndrome occurring in chronic glomerulonephritis. Moreover, the content of gamma globulins in chronic glomerulonephritis never reaches the values always found in multiple myeloma.

X-ray may reveal foci of lysis in the bones in multiple myeloma. Spherical defects in the skull and pelvic bones and osteoporosis of the spine are particularly characteristic findings. A typical increase in the number of plasma cells in the bone marrow is discovered in most cases by sternal puncture or drill biopsy of the iliac bone. It should be pointed out that these methods of examination allow the diagnosis of multiple myeloma to be made but do not identify the direct cause of the nephrotic syndrome.

Needle biopsy of the kidney must be conducted to resolve this last question. Its results are necessary not only for determining the exact character and severity of the kidney involvement, but for choosing the method of treatment.

The nephrotic syndrome is also encountered in other malignant tumours. It occurs most often in lymphogranulomatosis. The signs of the nephrotic syndrome disappear, as a rule, during a remission caused, for instance, by radiotherapy. It has been suggested that the tissue of the tumour produces antigens which may stimulate antibody production. Deposits of the antigen, antibody and complement are sometimes detected on the basal glomerular membrane of patients with malignant tumours, lymphogranulomatosis and carcinoma of the bronchus, mammary glands and intestine. A nephrotic syndrome occurring for the first time at an elderly age should be assessed as a possible manifestation of a malignant

Diabetic Nephropathy

The nephrotic syndrome in a patient with diabetes mellitus may develop under the effect of the disease itself or under the effect of drugs. Affection of the kidneys has become the main cause of the death of diabetics in the last 25 years. This circumstance explains the ever-growing interest in diabetic nephropathy. It is clinically manifested by proteinuria, oedema, and increased arterial pressure.

Proteinuria appears before the other signs of the syndrome. The degree of its intensity usually increases in direct proportion to the duration of diabetes. In continuously substantial loss of protein in the urine, hypoproteinaemia develops gradually because of a decrease in the concentration of albumin. The content of alpha-2 globulins and gamma globulins increases. The blood lipid and cholesterol content increases even in cases of uncomplicated diabetes.

Oedema, usually mild or moderate, is found in approximately half the patients who suffer from the disease more than 10 to 15 years. Massive nephrotic oedema is observed in 5 to 6 per cent of cases. Arterial pressure proves to be elevated in about half the patients by the time oedema appears. The incidence of arterial hypertension, just as the incidence of retinopathy and neuropathy, grows considerably in the later stages of the disease and is found in 90 per cent of far-advanced cases.

Progression of kidney insufficiency is attended by a decrease and later by the disappearance of glucosuria. Assessment of the severity of diabetes in such cases is based on the results of tests for blood sugar concentration. Diabetic glomerulosclerosis advances much more rapidly in young age than in elderly and aged persons. Survival from the time proteinuria appears ranges very widely. Death from renal insufficiency occurs three or four years after the development of the typical picture of the nephrotic syndrome, on the average.

Diabetic glomerulosclerosis is only one of the forms of kidney involvement in diabetes mellitus. Proteinuria, oedema, leucocyturia and erythrocyturia may be a consequence of heart failure, pyelonephritis, and other renal diseases often encountered in these patients. The character of the renal lesions in diabetics may be reliably determined only by means of needle biopsy.

It should also be noted that it is difficult to distinguish affection of the kidneys in diabetic glomerulosclerosis from that in amyloidosis if the specimen is stained with haematoxylin-eosin. The task is made easier if thioflavine T and Congo red are used for additional staining. The homogeneous structure of hyaline deposited in diabetic glomerulosclerosis and the fibrillary structure of amyloid are easily seen in the stained specimens by polarized microscopy.

There is no difficulty in distinguishing diabetic glomerulosclerosis from pyelonephritis. Glomerulosclerosis is characterized by bilateral and pyelonephritis by unilateral involvement of the kidneys. One kidney is always affected more than the other in bilateral pyelonephritis. In diabetic glomerulosclerosis both kidneys are involved to an equal degree. The asymmetry and uniformity of the affection are easily demonstrated by isotope renography or excretory urography.

Renograms in diabetic glomerulosclerosis may be abnormal, but the abnormalities are the same in both kidneys. In pyelonephritis one kidney is involved to a greater extent than the other. The kidney that is more affected becomes freed of the contrast medium later than the less affected kidney. In glomerulosclerosis both kidneys are cleared of the contrast medium within the same period of time.

Other Causes

A clinical picture of the nephrotic syndrome with hypoproteinaemia, massive proteinuria, oedema, and collection of fluid in the cavities always develops in cases of gradually progressive thrombosis of the renal veins. The process may either be bilateral or unilateral with involvement of the main renal veins or their intrahepatic branches. Patients with kidney amyloidosis and the nephrotic syndrome of any aetiology are particularly predisposed to renal venous thrombosis. This is explained by increased blood coagulation in these diseases. The growth of a tumour (hypernephroma in particular) into the lumen of the renal vein also creates conditions for the formation of thrombi.

The diagnosis of thrombosis of the renal veins in patients with the nephrotic syndrome and kidney amyloidosis is based on the sudden intensification of erythrocyturia and proteinuria followed by noticeable and quite rapidly developing anasarca, sometimes with the appearance or increase of fluid in the cavities. Thrombosis of the renal veins must be considered in all cases of the nephrotic syndrome of unclear aetiology.

Increased venous pressure is a constant sign of constrictive pericarditis and severe heart failure. Far-advanced cases of both diseases are usually marked by moderate protein loss in the urine and hypoproteinaemia. Great amounts of protein are always lost with the stools in constrictive pericarditis. The amount lost is in direct proportion to the severity of the condition. Hypoproteinaemia in constrictive pericarditis develops under the effect of two factors: increased loss of blood plasma proteins into the gastro-intestinal tract and increased loss of protein into the urinary tract.

Proteinuria is sometimes relatively mild in severe nephrotic

syndrome developing in constrictive pericarditis. Hypoproteinaemia in such cases is evidently caused by increased loss of protein into the gastro-intestinal tract. Successful operative treatment for constrictive pericarditis leads to a fall of the venous pressure to a normal level and disappearance of the syndrome of increased protein loss into the gastro-intestinal tract and proteinuria. Oedema disappears at the same time.

At the turn of the century it was already established that marked oedema is sometimes induced by salts of heavy metals (mercury, bismuth, gold). A great number of drugs are now known, the use of which leads to the development of the nephrotic syndrome. Antispastics such as mesantoin, tridione (trimethadione), etc. are particularly notorious in this respect. The development of the nephrotic syndrome after medication with antidiabetic and antipodagric agents (tolbutamide, benemid, etc.) is encountered much less frequently. Oedema usually develops after prolonged use of drugs although cases have been described in which it forms after a single dose, for instance, of a mercury preparation.

The drug-induced nephrotic syndrome differs neither in clinical manifestations nor laboratory findings from nephrotic syndromes of other origin. If the cause of the syndrome is identified in good time, its signs become less manifest after the agent is discontinued and may disappear completely. Interstitial nephritis with progressive chronic renal insufficiency develops in very severe affection of the kidneys.

Cases of the nephrotic syndrome caused by the patient's hypersensitivity to plant and grass pollen, bee venom, and other foreign proteins are a matter of interest in principle. The syndrome develops during contact of the patient with the foreign proteins and ceases soon after these are removed. Identification of the allergic origin of the nephrotic syndrome calls for detailed study of the medical history and a number of provocation tests with the suspected antigens. The nephrotic syndrome sometimes develops after preventive immunization. Vaccines against smallpox, tetanus and poliomyelitis are considered particularly hazardous.

A growing number of reports have been made in recent times on the development of the nephrotic syndrome after kidney transplantation. The internist must obviously gain a thorough knowledge of this complication because the number of such operations will grow considerably in the near future.

Proteinuria often appears immediately after transplantation of the kidney. In most cases it is moderate, but sometimes it is marked. It usually disappears a few months after the operation. Neither the duration nor the pronounced character of this proteinuria is of prognostic significance. Its origin is attributed to ischaemia of the kidney during surgery. A more serious prognosis is determined

not by this transient proteinuria, but by protracted proteinuria, usually developing some time after the transplantation and heralding the onset of the post-transplantation nephrotic syndrome.

The amount of protein lost in the urine in this syndrome ranges widely. The serum protein composition changes with the gradual development of hypoproteinaemia, the content of albumin and gamma globulin diminishes noticeably, while the content of the second globulin fraction increases. The concentration of triglycerides and cholesterol grows noticeably. Brief periods of microhaematuria and pyuria are sometimes disclosed.

Fluid retention in the body is usually mild and can be regulated by means of diuretics. The arterial pressure is increased in approximately half the cases. Biopsy and autopsy show that the underlying factor of the nephrotic syndrome and progressive functional insufficiency of the transplanted kidney is the chronic non-taking syndrome or chronic glomerulonephritis.

The differential diagnosis between these processes is very difficult and sometimes cannot be made. It is interesting that the post-transplantation nephrotic syndrome develops much earlier and is much more frequent in recipients who had signs of this syndrome in the course of the principal (initial) disease.

Enteropathy with Excessive Protein Loss

Enteropathy with increased protein loss is a clinical syndrome consequent upon increased permeability of the blood capillaries of the gastro-intestinal mucosa to blood plasma proteins or upon the loss of lymph from dilated lymphatics into the gastro-intestinal tract. Its diagnostic signs are increased protein content in blood plasma and stools, anasarca, collection of fluid in the cavities, and emaciation which is often concealed by oedema. Enteropathy with increased protein loss is often combined with diarrhoea and the malabsorption syndrome. The clinical picture in such cases comprises the symptoms and signs characteristic of all three syndromes.

The blood plasma proteins are synthesized in the liver and the cells of the reticuloendothelial system. They are excreted from the body in the urine, digestive juices, tracheobronchial and genital secretions, milk, semen and sweat. The content of proteins in blood plasma is characteristically constant, which points to the existence of a mechanism the activity of which is responsible for the congruence of the rates of their synthesis and their breakdown;

20 to 25 g of blood plasma proteins is broken down and, consequently, also synthesized daily, which accounts for about 10 per cent of their total content in the body.

Albumins comprise the greater part of blood plasma proteins and for the main part determine the level of the colloidal osmotic blood pressure. About 10 to 15 g of albumin is broken down in the body daily. Approximately 70 per cent of this amount is broken down in the gastro-intestinal tract, 15 per cent in the liver, and 10 per cent in the kidneys. Endogenic breakdown of blood plasma proteins also takes place in the cells of other organs and tissues, but the quantitative aspect of this process has not been sufficiently studied as yet.

The constancy of the blood plasma protein composition is regulated in the following way. With a decrease in the content of albumin in the intravascular space a mechanism decelerating the rate of albumin breakdown in the cells of all organs is triggered. Albumins enter the blood from the interstitial space as a result of which their constant concentration in the vascular bed is ensured. The same mechanism acts when the rate of albumin synthesis in the liver decreases. Under its effect the decrease in the rate of albumin synthesis is paralleled by a decrease in the rate of its breakdown. The equilibrium between the rates of synthesis and breakdown is restored although at a lower level. The total amounts of albumins in the intravascular and extravascular spaces diminish.

Decelerated synthesis is the principal cause of hypoproteinaemia in starvation, in anorexia often developing in mental diseases and organic gastrointestinal diseases, in kwashiorkor often encountered in tropical and subtropical countries, and in marasmus occurring in infants in their first year of life due to severe malnutrition.

Special research showed that the rate of albumin breakdown noticeably decreases three to five days after a low-protein diet is prescribed. As soon as a normal diet is given albumin catabolism increases and reaches normal value in three weeks. The content of proteins in blood plasma decreases during starvation. There is a particularly sharp fall in the albumin content. The concentration of beta globulins is reduced, but to a far lesser measure than the content of albumins. The weight content in the blood of alpha-1, alpha-2 and gamma globulin fractions is normal but their percentage correlation is slightly increased. The blood fibrinogen concentration diminishes.

The colloidal osmotic pressure of blood plasma is mainly determined by the content of albumins in it. Hypoalbuminaemia typical of starvation if sufficiently manifest leads to the development of oedema and collection of fluid in the cavities. Hypoproteinaemic oedema forms first around the eyes and other regions with well developed subcutaneous tissue. In protracted oedema its distribution is governed by the law of gravity.

The rate of albumin synthesis also decreases when the number of hepatic cells decreases and their function is impaired under the effect of inflammation or drugs, and when the function of the operon of the hepatocytes or gene controlling its activity is disturbed. Albumin synthesis may also be decelerated as a consequence of impaired ribosome function. These mechanisms are responsible for hypoproteinaemia and hypoalbuminaemia in diseases of the liver.

In many diseases hypoproteinaemia is not a consequence of delayed synthesis of blood plasma proteins, but results from their escape from the blood capillaries into the gastro-intestinal tract.

In the stomach and small intestine they are exposed to the effect of digestive juices and are broken down to amino acids. Ultimately part of them are lost in the faeces and part are absorbed and, like the amino acids of dietary origin, utilized by the cells of the organs and tissues. The continuous escape of proteins from the blood stream is compensated for to a certain measure by their accelerated synthesis.

According to our data, the rate of albumin synthesis in enteropathies with increased protein loss is sometimes two and a half to threefold the rate of its synthesis in a healthy person. Nevertheless, in a disease of long duration or in particularly high permeability of the blood capillaries, the content of protein in the intravascular and interstitial spaces decreases. There is a particularly sharp reduction in the albumin fraction. The content of alpha-1 globulin fraction in blood serum is sometimes slightly increased, while the content of alpha-2 and beta fractions is not changed.

Protracted losses of gamma globulins from the blood stream are sometimes attended by hypogammaglobulinaemia. In some cases the content of all immunoglobulins in the blood is reduced, while in others there is a selective decrease in the concentration of some of them. A state of immunodeficiency develops, in no way differing from similar conditions studied in greater detail in the nephrotic syndrome and diseases of the lymphoid tissues.

Intestinal Lymphangiectasis

The term 'intestinal lymphangiectasis' designates an isolated affection of the lymph vessels of the small intestine marked by impaired flow of lymph from this organ. Other authors call this disease 'idiopathic hypoproteinaemia' or 'hypercatabolic enteropathy'.

A congenital form of this disease, whose origin is evidently no different from that of the congenital form of lymphatic oedema of the lower limbs, and an acquired form developing as a complication of protracted inflammation of the lymphatics of the small intestine or its mesentery, are generally distinguished. Filariasis and sensitization of the vessels to their own lymphocytes are named the causes of chronic inflammation (Kawai, 1973). Lymph drainage of the small intestine may be blocked by tumours of the regional lymph nodes or tumour metastases to the mesenteric lymph nodes.

On examination, the small intestine is found to be somewhat dilated. The wall of the affected loops is thickened and swollen, its outer surface is dull, and the lymphatics of the serous coat are drastically dilated. With the injection of a dye into them, a thick network of vessels overfilled with lymph appears on the surface of

the small intestine. Some of them have a diameter of up to 4 or 5 mm.

Biopsy of the small intestine always demonstrates dilated lymphatics of the mucous and submucous coats. Lipophages containing vacuoles in the protoplasm are often found in the lumen of the lymph vessels. More than one drastically dilated lymph capillaries are usually seen in each villus of the mucous coat, as a result of which the villi are thickened, while their apical parts are sometimes noticeably thickened and flattened. The cell composition of the mucosa is mainly represented by lymphocytes and plasma cells. Neutrophils and eosinophils are found in few numbers.

The disease begins in childhood in most cases. Anasarca forms for which there seems to be no cause. It may disappear for a short time. On reappearing, it becomes generalized. It is soon joined by ascites and sometimes by hydrothorax too. Weakness, rapid fatiguability, and apathy appear. Diarrhoea develops from time to time, but it is never the principal or the early sign of the disease. At first, the patient is usually sent for examination to the cardiological or nephrological department where it is found that he has marked hypoproteinaemia due to a reduced content of albumins for the most part. The blood cholesterol content is normal or low. Lymphopenia and moderate anaemia are often detected.

The patient does not experience shortness of breath despite marked oedema. In performing work requiring physical exertion he tires easily but does not suffer from shortness of breath. The heart is normal in size, and there are no signs of congestion in pulmonary circulation. The size of the liver often cannot be determined because of ascites, but venous pressure is normal and the subcutaneous veins of the neck are not dilated. The visible mucous membranes are pale but not cyanotic. Hypoalbuminaemia in heart failure develops only after many years of the disease and after decompensation had occurred several times; in intestinal lymphangiectasis, in contrast, hypoalbuminaemia is found during the first blood test, usually within the first month after oedema begins. The diagnosis of the heart failure syndrome can usually be ruled out during the first clinical examination of the patient.

The characteristic appearance of generalized hypoproteinaemic oedema attended by collection of fluid in the cavities indicates the need for considering its possible association with the nephrotic syndrome and, first and foremost, with oedema in kidney amyloidosis and in nephritis with minimum changes. Neither traces of protein, nor red or white cells are found in the urine of a patient with intestinal lymphangiectasis who had no history of some disease of the urinary tract.

Marked hypoproteinaemia and the consequent oedema and collection of fluid in the cavities are induced by proteinuria in the nephrotic syndrome. Since the results of repeated urinalyses are nor-

mal, the cause of hypoproteinaemia should be linked with the loss of blood plasma proteins into the gastro-intestinal tract. The quantitative assessment of these losses is best accomplished by prescribing an intravenous injection of one of the blood plasma proteins labelled with some radioactive substance, e.g. iodine, chromium, copper, niobium. It is our experience that radioactive human serum albumin is the most suitable agent for this purpose.

After intravenous injection of 25 mcCi of iodine-labelled radioactive albumin, the radioactivity of the faeces of a healthy person does not exceed 3 per cent of the dose injected. Radioactivity of the faeces of patients with intestinal lymphangiectasis is always higher. The results of test for radioactive albumin half-life are also of considerable diagnostic importance: in a healthy person it ranges from 14 to 24 days. The albumin breakdown in the body of a patient suffering from intestinal lymphangiectasis is noticeably accelerated.

There are no essential disorders in the absorption of nutrients in intestinal lymphangiectasis. Evidence of this are the normal results of tests for xylose and vitamin B_{12} tolerance. The assimilation of fat and the absorption of fatty acids are normal in most patients. The content of fat in the faeces and its splitting factor are also normal. Thus, intestinal lymphangiectasis is characterized by accelerated breakdown of blood plasma proteins and their increased loss into the gastro-intestinal tract, while assimilation and absorption of carbohydrates, fats and vitamins remain normal.

The results of X-ray examination of the small intestine are not very valuable in making the differential diagnosis. Moderate dilatation of the jejunum with thickening of its folds is usually found. The characteristic picture of the biopsy specimen of the small intestine described above is of decisive differential diagnostic significance. Biopsy of the small intestine is a manipulation that is safe for the patient and should therefore be conducted before kidney biopsy in cases where the diagnosis is not clear.

Hypoproteinaemia due to a decreased content in the blood mainly of albumins combined with oedema and collection of fluid in the cavities is often encountered in diseases of the liver; these diseases, however, are easily distinguished from intestinal lymphangiectasis by the results of routine clinical and laboratory methods of examination. Liver functions are not disturbed in intestinal lymphangiectasis, but are often abnormal in cirrhosis of the liver. Signs of portal hypertension occur only in diseases of the liver. Hypoalbuminaemia in diseases of the liver is caused by delayed albumin synthesis, whereas in intestinal lymphangiectasis this synthesis is noticeably accelerated.

Hypoproteinaemia with hypoalbuminaemia and oedema is a characteristic sign of alimentary dystrophy. Delayed blood plasma protein synthesis is its typical laboratory sign. In intestinal lymphan-

giectasis, the rate of albumin synthesis is always increased, a fact even reflected in one of the names of the disease, 'hypercatabolic hypoalbuminaemia'. Patients with intestinal lymphangiectasis also differ from patients with alimentary dystrophy in the medical history and outward appearance.

Two of our patients suffering from intestinal lymphangiectasis had a loose stool with steatorrhoea which, however, was quite moderate and could not have been the cause of hypoproteinaemia and oedema. Such cases of intestinal lymphangiectasis must be differentiated from the sprue syndrome which also may lead to hypoproteinaemia and oedema.

Sprue Syndrome

The term 'sprue syndrome' designates a condition consequent upon impaired absorption of nutrients from the small intestine and increased permeability of its capillaries to blood plasma proteins. In mild cases, its clinical picture comprises diarrhoea and disturbances in the absorption of nutrients. Signs associated with great losses of protein in the stools predominate in the clinical picture of severe cases.

These disorders in their classical form are encountered in tropical sprue. A similar disease in countries with a moderate climate is known as 'non-tropical sprue', 'coeliac disease', 'gluten enteropathy'. The sprue syndrome, indistinguishable from coeliac disease in clinical signs, may sometimes be the first manifestation of diffuse diseases of the connective tissue.

The sprue syndrome is currently regarded to also include aminopterin enteropathy, intolerance of alpha-1 and alpha-2 lactoglobulins and some other proteins of cow's milk, intolerance of proteins of goat's milk, and some other diseases encountered predominantly in childhood.

Coeliac disease (gluten enteropathy) is encountered more often in the internist's practice. The mechanism of its origin has not been ultimately clarified. The characteristic changes in the mucous coat in this disease can hardly be regarded specific, because they are also found in tropical sprue and in collagen sprue which are generally accepted as independent diseases.

Coeliac disease may begin at any age, but usually it sets in in childhood. Diarrhoea usually develops in the second year of the baby's life after grain flour had been added to the diet. If not treated, diarrhoea may persist throughout childhood. In some cases it appears for the first time at the age of five or six years. Dystrophy and retardation of growth continue in such cases till puberty, when all signs

of the disease vanish completely. The disease commonly recurs between the ages of 20 and 40.

In approximately 20 per cent of cases, it begins in maturity. In one of our patients diarrhoea and other clinical signs of coeliac disease appeared only at an elderly age. Just as in childhood, coeliac disease in adults takes an undulant course, exacerbations alternating with remissions resulting from treatment.

In 80 to 95 per cent of cases coeliac disease begins with diarrhoea which is joined by loss of body weight, rapid fatiguability, and muscular weakness. This is the first stage of the disease, in which there are severe disorders of intestinal function with no clinical signs of deficient electrolyte or vitamin absorption.

In severe cases, the stool is fluid, pale in colour, and frothy, with a sharp acrid odour. Its daily volume reaches four litres. It is passed 10 to 15 times daily. Its characteristic feature consists in the ability to float on the surface of water. Sharp abdominal distension, and the sound of splashing in the caecum appear simultaneously with diarrhoea in the greater half of patients.

In 5 to 20 per cent of patients suffering from the disease, the stool has a consistency like that of putty. It is hard to wash it from a basin because it is very sticky. Polyfaecalia and the greyish colour of the stool and its tendency to float on water because of the high content of fat and gas are considered characteristic features. Periods of constipation alternate with periods of a loose stool in some patients. Loss of body weight is determined by the severity and extent of the lesion. There is no loss of appetite and it may even be keener. Deficient absorption of nutrients is partly compensated for by their increased consumption. Anorexia developing during exacerbations of the disease may lead to emaciation within a few weeks. Rapid fatigue occurs in the early stages of the disease.

The appearance of the clinical signs of deficient absorption of electrolytes and vitamins indicates the onset of the next stages of the disease. It is easily diagnosed because diarrhoea is joined by anaemia, glossitis, purpura, bleeding from the nose, gums, and gastro-intestinal tract, skin hyperkeratosis, nocturnal polyuria, and muscular weakness. Diminished strength of the proximal muscles of the upper limbs, nocturnal polyuria, and tetany are particularly characteristic of these patients.

Coeliac disease without diarrhoea is usually not diagnosed till anaemia caused by malabsorption of iron, vitamin B_{12} and folic acid becomes sufficiently obvious. It is general knowledge that iron is absorbed in the proximal segment of the small intestine and anaemia therefore is of the iron-deficiency type in most cases. The proximal segments of the small intestine are the first to come in contact with gluten contained in the diet and are affected much more severely than the other intestinal segments. Vitamin B_{12} is absorbed

in the distal parts of the ileum. Deficiency of this vitamin is encountered only in the severest cases of coeliac disease with involvement of the proximal and distal parts of the small intestine.

Iron-deficiency anaemia is the earliest sign in 2 to 10 per cent of cases of coeliac disease. Leucopenia and thrombocytopenia develop in attendance to it when the process spreads to the distal segments of the small intestine. Malabsorption of iron and folic acid is joined in such cases by deficient absorption of vitamin B_{12} and calcium, which is manifested by paraesthesia, tetany, and osteoporosis, sometimes with spontaneous bone fractures. Deficient absorption of potassium is manifested by nocturnal polyuria and muscular weakness. Vitamin A malabsorption is diagnosed because of skin hyperkeratosis and day blindness; deficient absorption of vitamin K is recognized from hypoprothrombinaemia and a tendency to bleed.

In the severest cases of coeliac disease, the signs of deficient absorption of nutrients are joined by disorders of protein metabolism demonstrated by intensified escape of blood plasma proteins into the gastro-intestinal tract and their high excretion in the faeces. This results in hypoproteinaemia mainly due to hypoalbuminaemia. Oedema forms first on the dorsal surface of the foot, anasarca and collection of fluid in the cavities occur later. As in other enteropathies with excessive protein loss, the rate of albumin synthesis in patients with coeliac disease is increased.

X-ray examination in this period of the disease demonstrates changes in the small intestine which are all important in the differential diagnosis. The characteristic X-ray signs of coeliac disease are as follows: dilatation of the small intestine, thickening of its folds, coarsening or even complete disappearance of the relief of its mucous coat, and irregular distribution of barium with its accumulation in certain parts of the small intestine separated by areas devoid of barium. Dilatation is always more pronounced in the jejunum, and segmentation in the ileum.

The diagnosis and differential diagnosis of coeliac disease is made much easier using the results of needle biopsy. Coeliac disease is characterized by predominant affection of the mucous coat of the small intestine. In typical cases its surface seems to be smooth because there are no villi. The epithelial cells become cuboidal and even squamous at times, their protoplasm is basophilic, the nuclei lose their basal arrangement and the brush border of the villi often disappears. The crypts of the mucous coat become deeper. The number of non-differentiated cells and the number of mitoses in the crypts are characteristically increased. The number of lymphocytes and plasma cells in the lamina propria of the affected areas of the small intestine increases noticeably. An increased number of cells producing immunoglobulins M is a particularly characteristic sign.

All the listed clinical, X-ray and histological signs of coeliac disease disappear completely after the patient is given a diet free of gluten.

Oedema and ascites in coeliac disease are often combined with enlargement of the liver in which fatty infiltration is usually found. Although the indicated combination of signs is also often encountered in heart failure, the differential diagnosis between coeliac disease and heart diseases may be easily established at the patient's bedside. The main diagnostic signs distinguishing the sprue syndrome from heart failure are as follows: protracted undulent course of the disease; association of the disease with diarrhoea; dependence of remissions on a gluten-free diet; soft oedema; pale but not cyanotic mucous membranes and skin; normal size of the heart; normal ECG; absence of signs of congestion in pulmonary circulation.

Considerable emaciation combined with periods of diarrhoea is often encountered in alimentary dystrophy. In about 30 per cent of these patients, oedema is combined with hepatomegaly. Ascites develops much less frequently. Oedema and collection of fluid in the cavities occur in these patients under the effect of hypoproteinaemia and hypoalbuminaemia which are constant signs of alimentary dystrophy. Recurrent diarrhoea is induced either by a concomitant infection, most commonly, bacillary dysentery, or by irritation of the gastro-intestinal tract with coarse, inferior-quality foods.

Hypoproteinaemia in coeliac disease is a consequence of increased loss of protein through the gastro-intestinal tract. It belongs to the category of hypercatabolic hypoproteinaemias. Hypoproteinaemia and hypoalbuminaemia in alimentary dystrophy result from retarded synthesis of blood plasma proteins. If it is impossible to determine the rate of albumin synthesis, the differential diagnosis between alimentary dystrophy and coeliac disease may be made, and reliably at that, from the findings of the patient's examination. Signs of pellagra are very often found in alimentary dystrophy but never in coeliac disease.

Coeliac disease and intestinal lymphangiectasis have very many signs in common. Both are attended by oedema, hypoproteinaemia and hypoalbuminaemia. Diarrhoea may be absent in both diseases. It is easier to distinguish these diseases by their medical history, the findings of needle biopsy, the character of disorders in vitamin and electrolyte metabolism and the results of trial therapy.

Coeliac disease and intestinal lymphangiectasis begin in childhood. The appearance of oedema is unassociated with diarrhoea in intestinal lymphangiectasis, whereas in coeliac disease oedema always occurs after a more or less lengthy period of diarrhoea. Anaemia (iron- or vitamin B_{12} -deficiency) is encountered in every case of more or less severe coeliac disease. Signs of hypokalaemia, hypo-

calcaemia and the abnormal outer appearance of the mucous membranes and skin described above are encountered in these patients simultaneously with anaemia.

Anaemia is an extremely rare complication of intestinal lymphangiectasis. Oedema in this disease appears and exists for a considerable length of time while the composition of the red blood remains normal; this never occurs in coeliac disease. Disorders of calcium metabolism do not occur in intestinal lymphangiectasis, whereas disorders of potassium metabolism develop only under the effect of prolonged and regular medication with diuretics.

The results of X-ray examination are also of certain differential diagnostic value. Changes in the small intestine typical of coeliac disease are never encountered in intestinal lymphangiectasis. The small intestine is always only moderately dilated in intestinal lymphangiectasis and the relief of its mucosal coat, although it becomes coarser, does not vanish completely. In coeliac disease the transverse diameter of the jejunum is at times enlarged two- or threefold and may be 5 or 6 cm, while the relief of its mucosal coat cannot even be seen in some cases.

Needle biopsy may yield the most convincing information. Changes in the lymph vessels are always found in the biopsy specimen taken from a patient with intestinal lymphangiectasis, while characteristic signs of mucosal atrophy are found in a specimen obtained from a patient with coeliac disease. The results of trial gluten-free diet are no less convincing in making the differential diagnosis: this diet is absolutely ineffective in intestinal lymphangiectasis, but leads to the disappearance of all clinical and laboratory signs of coeliac disease.

Tumours of the Small Intestine

Rapid emaciation attended by anaemia, anasarca, ascites and diarrhoea is often encountered in primary tumours arising from lymphoid tissue in the wall of the small intestine. Either the entire or the greater part of the small intestine is involved in these tumours. This clinical picture occurs only in diffuse affection of the small intestine which is encountered particularly frequently in Arabs and other aborigine inhabitants of the Middle East. In other countries the disease is a much less frequent occurrence. Both females and males acquire it usually between the ages of 15 and 40.

Diffuse haematosarcoma (lymphosarcoma, lymphogranulomatosis) of the small intestine is manifested clinically by diarrhoea, steatorrhoea and progressive emaciation. Just as in coeliac disease, anaemia, hypoproteinaemia and hypoalbuminaemia develop, the content of calcium and potassium in the blood decreases and this

leads to the development of muscular weakness, nycturia and tetany. The absorption of fat-soluble vitamins is disturbed as a result of which the skin becomes dry and hypoprothrombinaemia occurs. Iron absorption is noticeably impaired, which is attended by the development of iron-deficiency anaemia. Absorption of folic acid and xylose is disturbed if the tumour extends to the proximal segment of the small intestine; the absorption of vitamin B_{12} is impaired if the ileum is involved.

The gradually progressing hypoproteinaemia and hypoalbuminaemia lead to the development of hypoproteinaemic oedema and ascites. Sometimes we noted a different correlation between the severity of oedema and ascites than that encountered in coeliac disease. This was evidently caused by early block of lymph flow from the small intestine. In coeliac disease, oedema develops much earlier than ascites, whereas in haematosarcoma of the small intestine ascites may form either before oedema or simultaneously with it.

The similarity with coeliac disease is also seen in the favourable effect produced by corticosteroid hormones on the pronounced character mainly of the subjective signs of the disease. The condition of most patients with lymphosarcoma of the small intestine improves temporarily if corticosteroids and anabolic steroids are given in the early stages of the disease. Diarrhoea and anaemia diminish for some time and the patient gains in weight. If we should add that the X-ray signs of diffuse lymphosarcoma of the small intestine may be no different from those in coeliac disease it will become obvious how difficult it is to distinguish these diseases.

Diffuse lymphosarcoma of the small intestine is usually misdiagnosed as coeliac disease at the very beginning of the disease because there is usually no extraintestinal manifestations of the tumour. The findings of a clinical follow-up allow the correct diagnosis of the disease to be made only in the late stages of it. The signs appearing in the late stages are a palpable tumour in the abdomen and complications caused by it (gastro-intestinal haemorrhage and perforation of the intestine with the development of peritonitis).

Long-term subfebrile body temperature is quite often observed in lymphosarcoma, but never in uncomplicated coeliac disease. Growth of the tumour is often attended by more or less intensive abdominal pain. In coeliac disease, marked abdominal distension is usually unattended by pain.

These two diseases differ noticeably in their course. Patients with lymphosarcoma usually die within the second year after the appearance of diarrhoea, anaemia and oedema, whereas patients with coeliac disease survive for a much longer period, as a rule. In typical cases, coeliac disease begins in childhood and after a long-term remission recurs at a mature age. Medication with corticosteroids in lymphosarcoma may cause a remission, but this remission

is always shortlived and it only occurs once. Patients with a malignant tumour of the small intestine have a poor appetite and develop anorexia in the later stages of the disease. In coeliac disease the patient's appetite is usually good. It is only lost for some time during severe exacerbation.

Needle biopsy is valuable only when it is possible to obtain a piece of the mucosa from the intestinal area involved in the tumour. A negative result of examination of the biopsy specimen does not rule out the diagnosis of lymphosarcoma. The mucosal coat in these areas is flattened, its crypts are elongated and the villi are small. Signs by which it can be distinguished from the mucosa in coeliac disease are few in number: a lesser number of Lieberkühn's crypts, abnormal architecture of the lymph follicles, and copious round-cell infiltration of the lamina propria mucosae and the appearance of blast cells in it.

Trial therapy with a gluten-free diet is the most reliable method of differential diagnosis. It always causes a remission in coeliac disease, but is always ineffective in lymphosarcoma of the small intestine.

Whipple's Disease

In 1907 Whipple described a systemic disease in which Gram negative bacilli were found in the affected organ during exacerbation. This disease was eventually named after him. The clinical manifestations of Whipple's disease comprise fever, polyarthritis, excessive loss of protein into the gastro-intestinal tract, malabsorption of nutrients, anaemia, lymphadenopathy, pleurisy, endocarditis, loss of memory, and brown pigmentation of the skin. Death occurs if no treatment is applied. With the introduction of antibiotics in the treatment of this disease, fatal cases have become a rarity.

Involvement of the small intestine is found in all cases of Whipple's disease and its wall is thickened and oedematous when examined during operation. Thickened wide villi are found on the surface of the mucosal coat. In severer cases, the mucosa is devoid of villi and is no different from the mucosa in coeliac disease in appearance.

Microscopy discloses marked infiltration of the lamina propria mucosae by large macrophages containing a large number of glycoprotein granules in the protoplasm. The number of plasma cells, lymphocytes and eosinophils in the lamina propria is much less than in a healthy person. Electron microscopy reveals a great number of bacilli existing freely between the cell elements of the lamina propria mucosae.

Whipple's disease is encountered at any age, but it usually begins between 30 and 50 years. The incidence among males is eight- to tenfold that among females. The clinical manifestations of the disease are diverse. The disorientation of the patient as to time and place and loss of memory come to the forefront in affection of the central nervous system. All our patients had a strikingly diffuse brown pigmentation of the skin which in combination with weakness and hypotension suggested a concomitant affection of the adrenals.

In about 75 per cent of cases the disease begins with fever which is joined by arthralgia and polyarthritis. Body temperature is usually subfebrile, but during an episode of polyarthritis it rises to 38-39°C and is often attended by chills. Both large and small joints are affected. Sharp pain is sometimes experienced in the back, evidently because of the involvement of the vertebral joints in the process. Migration of the affection, sharp tenderness of the involved joints, and the absence of a tendency to cause deformities are typical features. Simultaneously with affection of the joints there is enlargement of the cervical, axillary and inguinal lymph nodes which, in contrast to the joints, are non-tender and freely mobile on palpation.

Affections of the small intestine, serous membranes, and heart develop in most cases in attendance to fever and polyarthritis, although sometimes they may be the first manifestations of the disease. The small intestine is involved in all far-advanced cases of Whipple's disease. Polyserositis and endocarditis are encountered much more rarely. The appearance of oedema in affection of the heart is attributed to heart failure and in affection of the small intestine to hypoproteinaemia. The latter is caused by impaired digestion and absorption of the nutrients and increased loss of protein in the faeces. Hepatomegaly in the first case is explained by heart failure, in the second—by its steatosis.

As in the other cases with the malabsorption syndrome, in Whipple's disease the stool may be fluid or soft. Its grey colour and a sharp fetid odour are explained by steatorrhoea. In the cases we dealt with, the stool was passed three to six times daily. Cases of Whipple's disease marked by constipation are known. The stool of all our patients was loose or soft. In distinction from coeliac disease, in Whipple's disease diarrhoea is usually combined with anorexia and abdominal colics.

Long-term diarrhoea with excessive loss of protein in the faeces leads to the development of cachexia, hypokalaemia with muscular weakness characteristic of it, hypocalcaemia and deficiency of fat-soluble vitamins. Malabsorption of iron, xylose, folic acid and vitamin B_{12} underlies anaemia which is always encountered in severe cases of Whipple's disease. Affection of the central nervous system

is the result of the direct effect of the causative agent on it.

Whipple's disease most often must be differentiated from coeliac disease. Both are marked by diarrhoea, anaemia, cachexia, oedema, and severe muscular weakness. We are of the opinion that due consideration of the following problems will allow these diseases to be differentiated with assurance.

They differ sharply in their course. Coeliac disease begins in childhood in most cases and prevails among females. A recurrence of the disease occurs at young age and in maturity after a lengthy remission. Whipple's disease may set in at any age and begins with fever and polyarthritis, but not with diarrhoea. Diarrhoea appears about four or five years after polyarthritis. In Whipple's disease, diarrhoea is never encountered without polyarthritis.

Extraintestinal manifestations of coeliac disease comprise signs of the malabsorption syndrome and the syndrome of excessive loss of protein in the faeces. The extraintestinal manifestations of Whipple's disease are of a greater variety and are not restricted to these two syndromes. If the syndrome of fluid collection in the pleural cavity can be accepted as a manifestation of hypoproteinaemia, and the precardial systolic murmur can be explained by anaemia, enlargement of the lymph nodes, in contrast, remains a syndrome for which no explanation is satisfactory. Body temperature is usually normal in coeliac disease but subfebrile in Whipple's disease in which even fever is encountered during exacerbation.

Even in the severest cases of coeliac disease the patient retains clear consciousness and willingly converses with the physician, providing all the information on the course of the disease of interest to the doctor. The patient's behaviour is always fitting for the circumstances. A patient suffering from Whipple's disease in the stage when oedema and diarrhoea appear cannot give a detailed description of past diseases or of the course of the current disease because of his acute lapses of memory. His behaviour is not adequate to the circumstances and signs of disturbed function of the cranial nerves are evident.

Trial therapy with gluten-free diet is highly effective in coeliac disease but does not influence the course of Whipple's disease. Antibiotics (penicillin, tetracycline, etc.) in Whipple's disease bring relief from fever and pain in the joints within a few days. Diarrhoea usually disappears in two to four weeks.

Needle biopsy yields the most valuable differential diagnostic information. Light microscopy reveals infiltration of the lamina propria mucosae by macrophages, characteristic of Whipple's disease, in the biopsy specimen. Repeated biopsy shows that the macrophages disappear from the lamina propria of the small intestine a few days after the beginning of antibiotic therapy. The results o

biopsy of an enlarged lymph node may also prove valuable in making the diagnosis.

The intestinal syndromes of diffuse lymphosarcoma of the small intestine and Whipple's disease hardly differ, and in making the differential diagnosis one should therefore take into account the extraintestinal manifestations of these two diseases. Fever is usually moderate throughout the whole course of lymphosarcoma; it is also moderate in most cases of Whipple's disease, but in taking the medical history it may sometimes be established that the patient suffered periods of high fever attended by chills. Arthralgia is a most frequent symptom of Whipple's disease but is rare in primary lymphogranulomatosis of the small intestine and is practically never encountered in lymphosarcoma of the intestine.

Enlargement of the lymph nodes is a frequent occurrence in Whipple's disease and may also occur in lymphogranulomatosis and lymphosarcoma. Biopsy of the enlarged node often has a decisive influence on formulating the diagnosis. Fluid accumulates in the cavities in both diseases, ascites is nevertheless always mild in Whipple's disease but may be quite large in lymphosarcoma. Moreover, in lymphosarcoma it usually forms before fluid accumulates in the pleural cavities.

Gastro-intestinal bleeding and perforation are characteristic complications of lymphosarcoma but never occur in Whipple's disease. Disturbed psyche and impaired memory are typical of Whipple's disease, but not encountered in lymphosarcoma. Antibiotic therapy completely relieves all the clinical manifestations of Whipple's disease but produces absolutely no effect on the course of lymphosarcoma.

In generalizing the data discussed, it may be stated that it would be expedient to divide the forms of oedema which are probably of the same origin into two groups differing in the ways of protein loss from the body. The clinical picture of the nephrotic syndrome develops when protein is lost through the urinary tract. Loss of protein through the gastro-intestinal tract leads to the development of enteropathy with excessive protein loss, a syndrome that has not been sufficiently studied as yet. It is advisable to regard these syndromes as separate clinical entities, because they differ in their clinical manifestations, in prognosis, and in the method of treatment. They may be distinguished by the results of clinical urinalysis. The diagnosis of the different clinical forms within each syndrome may be made in many cases only from the results of a clinical follow-up and of many special methods of examination.

Supplement XVIII-1

Causes of Oedema

1. Oedema occurring under the effect of local factors.
   Lymphatic oedema.
2. Premenstrual syndrome and oedema in pregnancy.
3. Nephrotic syndrome.
   Glomerulonephritis.
   Amyloidosis.
   Diabetic nephropathy.
   Other causes.
4. Enteropathy with excessive protein loss.
   Intestinal lymphangiectasis.
   Sprue syndrome.
   Tumours of the small intestine.
   Whipple's disease.
5. Heart failure.

Supplement XVIII-2

Causes of the Nephrotic Syndrome

1. Glomerulonephritis.
   Chronic glomerulonephritis of unknown aetiology.
   Diffuse diseases of the connective tissue.
      Systemic lupus erythematosus.
      Rheumatic fever.
      Scleroderma.
      Dermatomyositis.
      Rheumatoid arthritis.
   Systemic vasculitis.
      Haemorrhagic vasculitis.
      Periarteritis nodosa.
   Infectious diseases.
      Bacterial endocarditis lenta.
      Malaria.
      Pyelonephritis.
2. Amyloidosis.
   Secondary.
   Familial.
      Periodic disease.
      Other congenital diseases.
   Malignant tumours.
3. Diabetic glomerulosclerosis.
4. Other causes.
   Constrictive pericarditis.
   Heart failure.
   Thrombosis of renal veins.
   Drugs.
   Plant pollen.
   Transplantation nephrotic syndrome.

Chapter XIX

Paroxysmal Dyspnoea

For the purpose of differential diagnosis it is expedient to distinguish dyspnoea according to the clinical course, applying the criteria which can be easily detected at the patient's bedside, rather than according to the mechanisms of its origin. We distinguish dyspnoea occurring mainly on effort and dyspnoea developing in paroxysms during physical exercise, after it or irrespective of it. This chapter discusses the differential diagnosis only of those diseases which are complicated by attacks of paroxysmal dyspnoea. In some cases these attacks develop in a person who is in sound health. After they cease the patient has no complaints and experiences no difficulties in respiration. In other cases the attacks occur as a complication of a disease which is marked by permanent dyspnoea. In the practice of an internist, attacks of paroxysmal dyspnoea are mostly encountered in diseases of the lungs and cardiovascular system.

Diseases of the Lungs

An attack of paroxysmal dyspnoea in a previously healthy young or middle-aged person is most often the beginning of **bronchial asthma.** Most contemporary clinicians distinguish three types of bronchial asthma. Atopic bronchial asthma is induced by antigenic stimuli entering the bronchial tree from the external environment. The disease begins, in most cases, between the ages of 3 and 45 years and is caused by allergens brought into the bronchial tree with the air. The blood immunoglobulin E content in these patients is increased as a rule. Infectious bronchial asthma occurs with no obvious cause in some cases. In the opinion of most clinicians, it is most likely caused by a chronic infection of the bronchial tree. The nature of the infection often remains unidentified. The disease usually sets in before the age of 5 or after the age of 35 years, and follows a severe course. Mixed bronchial asthma is spoken of in those instances when the simultaneous activity of the allergic and the infectious factors is presumed.

The mildest attacks of bronchial asthma are manifested by a dry cough. Respiration may remain vesicular with no attendant respiratory murmurs. In severer cases breathing becomes difficult. Cough

is attended by discharge of a small amount of mucous sputum. A small number of dry sibilant rales are heard during expiration. During a severe attack of paroxysmal dyspnoea the patient is compelled to sit down. The sputum becomes glassy and viscous and often contains mucous plugs. A large number of dry sibilant rales are heard during slow expiration. A sharp decrease in the number of rales, or their almost complete disappearance ('silent lung') is encountered during extremely severe attacks of paroxysmal dyspnoea usually a while before hypoxic coma. The appearance of purulent sputum indicates that an attendant infection of the bronchial tree has developed. Bronchial asthma is characterized by reversibility of the bronchospasms, i.e. change of the periods of drastic bronchial obstruction to periods in which bronchial patency becomes normal or almost normal.

A clinically indistinguishable attack of paroxysmal dyspnoea sometimes develops in repeated exposure of the patient to some drugs. This **drug-induced bronchospasm** is usually combined with lesions of the skin and mucous membranes. Rhinitis is considered to be a particularly characteristic condition. Bronchospasms sometimes develop in **ascariasis, strongyloidiasis, opisthorchiasis** and **other parasitic diseases of the lungs** at a certain stage of their development.

Attacks of paroxysmal dyspnoea are a constant occurrence in **bronchopulmonary aspergillosis** which is almost always caused by *Aspergillus fumigatus* and *Aspergillus niger* species. Both fungal species are found in the upper respiratory tract. They are a particularly common finding in the sputum of patients with bronchial asthma. In diminished body resistance, e.g. in medication with corticosteroids, antibiotics, and cytostatics, these saprophytes invade the tissues. Mucous plugs composed of aspergilli and eosinophils are found in the secretions of the segmental bronchi in such cases. Dyspnoea, leucocytosis with an increased eosinophil count in the blood, fever, and cough with purulent expectorations often containing mucous plugs of fungi and eosinophils are encountered in most patients. Many patients show a positive skin reaction to the introduction of an extract of the aspergilli and a positive precipitation reaction in high titres. The co-existence of mycetoma and allergic aspergillosis is sometimes encountered. X-ray examination of patients with this form of aspergillosis often demonstrates homogeneous shadows of equal density along the length of the bronchi. The upper pulmonary lobes are involved in most cases. Centrally located bronchi are affected more frequently and intensively than the peripheral bronchi. Rapid disappearance of the shadows is characteristic, although in some cases they persist for weeks and even months. Atelectases of pulmonary segments adjacent to the bronchus develop sometimes. The bronchi remain distended after

recovery as a rule. Cylindrical bronchiectases are more common than sacculated bronchiectases.

Paroxysmal dyspnoea in patients with **chronic bronchitis, chronic pneumonia** and **obstructive pulmonary emphysema** occurs as the result of bronchospasm and narrowing or even total obstruction of the bronchi by viscous secretions. The formation of atelectases in such cases leads to dyspnoea, cyanosis, and tachycardia. The development of attendant infection is manifested by fever. The physical signs of pulmonary infiltration are frequently undetected; roentgenoscopy demonstrates microfocal shadows usually in the lower lobes of the lungs. In distinction from bronchial asthma, the bronchi in these diseases are obstructed not only during the attack of paroxysmal dyspnoea but also in the period between attacks.

Paroxysmal dyspnoea also develops in **mechanical obstruction of the bronchi by a foreign body,** a sagging posterior membranous wall of the trachea and large bronchi **(tracheo-bronchial dyskinesia), bronchial tumour** or in compression of the bronchi by rapidly growing lymph nodes, e.g. in **bronchiadenitis, lymphogranulomatosis** and **tumour metastases.** The attacks of dyspnoea in these patients are very severe and do not respond to the commonly applied antiasthmatic therapy. Attacks of paroxysmal dyspnoea occur in accidental or **occupational irritation of the trachea and bronchi.** An adequately taken medical history allows these conditions to be differentiated from bronchial asthma without any difficulty. Respiratory disorders in **neurocirculatory asthenia** and **hysteria** are usually marked by hurried shallow breathing and laryngospasm.

The paroxysm of dyspnoea in **spontaneous pneumothorax** arises suddenly following pain in the affected side of the chest. After that, the pain and dyspnoea are experienced together. By the end of the first 24 hours dyspnoea decreases as a rule and the patient's condition improves noticeably. The physical signs of pneumothorax (tympany elicited by percussion, diminished respiration, displacement of the heart) are insufficiently clear in some cases. The diagnosis of spontaneous pneumothorax is made with assurance only when the line of the visceral pleura is clearly demonstrated on X-ray. When the clinical findings suggest this diagnosis with high probability but the X-ray findings are not clear it is advisable to examine the patient when he is lying on his side. The free air then rises to the lateral wall of the chest and the conditions for its demonstration become much better.

Spontaneous pneumothorax takes a favourable course in most cases. Valvular pneumothorax develops sometimes in injury to the lung, bronchial carcinoma, and pneumonia. The volume of air in the pleural cavity gradually grows and the patient's condition becomes very grave. Tympany is produced by percussion only at the onset of this type of pneumothorax. Later, with the gradual accu-

mulation of air in the pleural cavity, percussion over the affected lung elicits less resonant tympany. In combination with diminished breathing a picture resembling that of accumulation of fluid in the pleural cavity is produced. The X-ray signs of pneumothorax are always well demonstrated in such cases. Spontaneous pneumothorax is most commonly encountered in males of 20 to 40 years of age. The right lung is involved somewhat more frequently than the left. Recurrences are common. Recurrent pneumothorax develops on the same side in 30 per cent of cases and on the contralateral side in 10 per cent of cases.

Diseases of the Cardiovascular System

Many diseases of the cardiovascular system are complicated by attacks of dyspnoea which may result in pulmonary oedema in severe cases. The mechanisms of shortness of breath and paroxysmal dyspnoea in bronchial asthma differ from those in heart diseases, but the arising clinical pictures are sometimes very similar and the differential diagnosis is very difficult. It will be much easier to overcome these difficulties for a physician with a sound knowledge of the patterns of the development of pulmonary oedema in diseases complicated by left-ventricular failure.

Haemodynamic disorders in **acute left-ventricular failure** lead to interstitial oedema and oedema of the pulmonary air ways of two types. *Interstitial oedema* is recognized by the thickening of the pulmonary interlobular septa. Its clinical signs are inconstant and therefore not always revealed by physical examination. Patients complain of shortness of breath, orthopnoea and dry cough, but the respiratory sounds remain unchanged because fluid is present in the interstitial space. The X-ray signs of interstitial pulmonary oedema are more constant than the clinical signs. *Alveolar oedema* of the lungs always develops later than interstitial oedema. It is recognized on the radiograph by lobular shadows which are occasional or merged and form shadows of irregular shape with blurred borders. These shadows are scattered at random in both pulmonary fields. The following pattern can be traced: the closer to the pulmonary root, the larger and more densely grouped are these shadows. In other cases oedema of the pulmonary airways is found in the zones surrounding the roots of the lungs and produces a homogeneous shadowing in the shape of a butterfly or bat's wings. The peripheral parts of the lung are not involved in oedema.

The first type of oedema of the pulmonary airways described above is always manifested clinically by severe dyspnoea which

develops into orthopnoea as a rule. Cough may be dry at the onset of the disease, but later frothy sputum is produced in great amounts which may be colourless or pink, or it may contain a small admixture of blood. Attacks of *cardiac asthma* occur during physical exertion or soon after it. Sometimes they arise at night, probably because of the increased blood filling of the lungs at this time, which is attributed to changes in the tone of the vegetative nervous system and change in the patients' position in bed. Most patients suffer greatly from this condition; they are cyanotic and gasp for air; the skin is covered with cold, sticky sweat. Tachycardia occurs. Sonorous crepitation and sonorous moist rales are heard at first only over the lung base and later over the entire surface of the lung. Most patients have increased venous pressure (which is determined from the swelling of the subcutaneous veins on the neck), an enlarged liver, anasarca, and other signs of heart failure.

Oedema of the pulmonary airways producing a butterfly shadow around the root causes the same clinical picture as diffuse interstitial oedema. Despite the massive and usually homogeneous shadowing of one half or even two thirds of the medial parts of the lungs, patients may have no complaints and examination reveals normal respiratory sounds. Rales often cannot be detected even in patients who complain of dyspnoea and in whom orthopnoea is observed. These discrepancies between the results of clinical and X-ray examinations are explained by the fact that the pulmonary areas around the root do not play any decisive role in the gas exchange which mainly takes place in the peripheral parts of the lung.

Paroxysmal dyspnoea may develop both at rest and on effort. It always begins acutely. Attacks of paroxysmal dyspnoea at night or coughing fits are particularly characteristic of left-ventricular failure. In typical cases the patient wakes up at night with the feeling that there is not enough air. He sits in bed or gets up, walks to the window and opens it so as to take a deep breath of fresh air. In about half an hour the patient feels better and returns to bed. He may sleep without any further disturbance till morning, or may be awakened in two or three hours by a recurrent attack of paroxysmal dyspnoea. Severe attacks may develop into pulmonary oedema which is marked by expectoration of large amounts of frothy sputum and moist sonorous rales in the lungs.

During paroxysm of dyspnoea the patient feels much relieved when he changes from a lying to a sitting position because this is always attended by a decrease in the flow of venous blood to the heart and in the blood hydrostatic pressure in the upper parts of the lung and by an increase of their vital capacity. During particularly severe paroxysms the patient can only sit. With the gradual development of heart failure orthopnoea sometimes disappears. This is explained by a decrease in the blood filling of the lungs

because of concomitant right-ventricular failure. Pulmonary hypertension protects the lung capillaries from increased blood pressure and contributes to the disappearance or abatement of orthopnoea. With the development of right-ventricular failure, general weakness and oedema but not dyspnoea prevail in the picture.

The long-term (at times many years long) history of paroxysms of dyspnoea should be regarded as a very convincing argument in favour of bronchial asthma. In bronchial asthma dry sibilant rales are heard in both lungs during inspiration and expiration, during an attack and after it; in cardiac asthma they are heard only during the attack. X-ray examination of the patient after an attack of cardiac asthma often discloses signs of pulmonary interstitial oedema which appear somewhat earlier than the episodes of paroxysmal nocturnal dyspnoea. Moist, fine-bubbling, dull rales are often heard in the lower part of both lungs during an attack of cardiac asthma. They disappear when the attack ends. In pulmonary oedema the sputum is frothy or pink and is expectorated during the attack. In bronchial asthma sputum is expectorated only at the end of the attack. In cases of non-complicated bronchial asthma it is discharged in a small amount and has a glassy consistency; a large number of Curschmann's spirals, eosinophils and Charcot-Leyden's crystals are found in it by microscopy.

Much differential significance should also be attached to the absence of some signs, for instance, the absence of a history of diseases of the cardiovascular system. A paroxysm of dyspnoea in a healthy young person who never had a heart disease and has a normal or moderately increased heart beat rate is probably an attack of bronchial asthma. It is also general knowledge that cardiac asthma and pulmonary oedema are never encountered in stenosis of the pulmonary artery, cor pulmonale or constrictive pericarditis.

Left-ventricular failure underlies most cases of cardiac asthma. Its most common causes are (see Supplement XIX-1): diseases of the myocardium and valvular apparatus of the heart and disorders in the rate and rhythm of cardiac contraction. In **hypertensive disease** paroxysms of dyspnoea occur under the effect of acute left ventricular failure. These paroxysms are characteristically brief they usually last 15 to 30 minutes and cease spontaneously. The attack begins during hypertensive crisis. The number of moist rales in the lungs grows very rapidly, but the classical picture of pulmonary oedema with frothy expectorations does not develop in cases uncomplicated by myocardial infarction. In our experience we encountered a delicate diastolic murmur of aortic insufficiency after the attack which disappeared leaving no trace two to four days after the crisis.

Left-ventricular failure is particularly common in **diseases of the heart muscle.** A long paroxysm of dyspnoea is among the characteris-

tic symptoms of *gross myocardial infarction*. This assertion is true only of primary infarction. Status asthmaticus is sometimes encountered in small recurrent infarctions. Moreover, orthopnoea and pulmonary oedema may develop in *left-ventricular aneurysm and gross postinfarction cardiosclerosis* even without fresh necrosis. Nevertheless, each attack of dyspnoea in these patients should be assessed as a possible consequence of a fresh necrosis and examination aimed at its detection should always be undertaken. Focal lesions in such cases are usually found either in the subendocardial coat of the left-ventricular anterolateral wall or in the interventricular septum on the side facing the left ventricle. The final diagnosis is made from comparing the results of repeated clinical and laboratory examinations.

The diagnosis of microfocal myocardial affection is more substantiated if the characteristic ECG changes after an attack of paroxysmal dyspnoea are attended by increased creatine phosphokinase activity and increased concentration of protein-carbohydrate complexes in the blood. A deep *T* wave may be recorded on repeated electrocardiograms in such cases. In appraising the results of instrumental examination, it should be taken into account that a depressed *ST* segment in left chest leads or only in leads V_5 and V_6 and in standard leads I and II may be a consequence of treatment with cardiac glycosides. Depressed *ST* segment and negative *T* wave in left chest leads are often found in left-ventricular hypertrophy. True, the *T* wave in such cases is asymmetrical and has a rounded apex. The *ST* segment in left chest leads is also depressed during treatment with quinidine and other anti-arrhythmic agents. Study with the use of technetium pyrophosphate demonstrates a new focus of necrosis in the myocardium. Echocardiography helps in disclosing foci of dyskinesia in the myocardium. The main difficulty consists in establishing the time of its origin. This subject is discussed in greater detail in the chapter 'Chest Pain'. Paroxysms of dyspnoea are often among the earliest manifestations of **myocarditis** and progressive **cardiomyopathy.**

Valvular heart diseases are often complicated by attacks of cardiac asthma. It is a particularly constant occurrence in *aortic stenosis.* In this disease dyspnoea at first occurs on mild physical exertion and is attended by dizziness or retrosternal pain. Fits of tormenting cough at night are often the earliest sign of developing left-ventricular failure. Typical attacks of nocturnal paroxysmal dyspnoea which may terminate in pulmonary oedema may develop in graver cases. Interrogation of the patient usually discloses the association of these attacks with effort. They may occur during or a few hours after physical exertion. Arterial pressure may be reduced, normal or elevated during the attack. In most of our cases with aortic stenosis arterial pressure was elevated during an attack of cardiac asthma.

Orthopnoea develops sometimes. Depending on the severity of the patient's condition, it lasts a few hours to several days. Pain in the region of the heart of various duration and intensity develops at the same time as orthophoea in most instances. In cases with a fatal outcome, autopsy reveals very many small foci of necrosis in the subendocardial coat of the left ventricle. They most probably form during paroxysms of dyspnoea and orthopnoea; that is why particular attention should be paid to the body's general reaction after the attacks. In mild cases body temperature, the leucocyte count and ESR do not change. Attacks of cardiac asthma in patients with *aortic insufficiency* may be attended by perspiration which is so profuse that drops of sweat run down the body.

Sudden paroxysm of dyspnoea of several hours to several days predominates in the clinical picture of *acute mitral insufficiency* which is quite often mistaken for aortic stenosis. Acute mitral insufficiency occurs in a healthy person as a result of *rupture of the mitral valve tendinous chordae.* Such ruptures occur much less frequently in bacterial endocarditis, during mitral commissurotomy, in myocardial infarction, Marfan's syndrome, osteogenesis imperfecta, myxomatous degeneration of the mitral valve cusps, and in some other rare diseases.

In typical cases paroxysmal dyspnoea and sometimes pulmonary oedema occur in a healthy man during physical effort. Auscultation reveals a loud scraping systolic murmur and systolic tremor in the precordial region. The systolic murmur is clearly transmitted to the vessels on the neck and is often mistaken for the aortic stenosis murmur. The patient assures the doctor that he had never suffered from rheumatism and that neither heart disease nor systolic murmur had been previously found. Study of his case record in the outpatient clinic confirms that before the development of paroxysmal dyspnoea the size of his heart had been normal while the heart sounds had been clear and pure. Physical and X-ray examination shows that after the onset of dyspnoea and the origin of a coarse systolic murmur the dimensions of the heart and (which is most important) the size of the left atrium remain normal as before.

Myocardial infarction with affection of the papillary muscles of the heart usually begins as status asthmaticus which in particularly severe cases terminates in oedema of the lung. Acute mitral insufficiency in this type of infarction is mostly consequent upon inability of the affected papillary muscle to hold the valve cusp in place. In rare cases the tendinous chordae are torn from the site of their attachment to the apex of the papillary muscle. Ruptures of the tendinous chordae are encountered infrequently as a *complication of bacterial endocarditis, sarcoidosis* and *dermatomyositis.* Mitral insufficiency is diagnosed from the sudden appearance of a loud systolic murmur and orthopnoea.

Paroxysmal dyspnoea in patients with severe *mitral stenosis* not attended by right-ventricular failure is primarily caused by obstruction to the blood flow at the level of the left atrioventricular orifice. Pressure in the pulmonary artery sharply elevates in these patients during physical exertion, which induces transudation of fluid into the interstitial tissue of the lung. The paroxysms of dyspnoea in these patients are often complicated by pulmonary oedema. In mitral stenosis complicated by severe and protracted heart failure, paroxysmal dyspnoea is usually caused by embolism of the pulmonary vessels and lobular pneumonia which is usually peri-infarct in character. The veins of the pelvis and lower limbs are the common source of the embolism. Obstruction of the small pulmonary arteries is manifested not by infarction of the lung, but by an attack of dyspnoea or rather by status asthmaticus followed in some cases by moderate leucocytosis, increased ESR, tachycardia and intensification of heart failure. X-ray sometimes discloses lobular pneumonia (peri-infarct).

A paroxysm of **supraventricular tachycardia** and **tachyarrhythmia** is attended in many cases by orthopnoea and sometimes leads to pulmonary oedema. Whether or not an attack of dyspnoea occurs during the paroxysm of tachycardia is determined by the interrelationship of the following three factors: the initial functional condition of the heart, the duration of tachycardia, and the rate of cardiac contractions. Tachycardia of 180 beats per minute in patients with a healthy heart may continue for one and even two weeks and cause only a complaint of palpitation. In patients with valvular heart diseases and especially in those with mitral stenosis a sharp drop in the minute volume occurs in a much lower heart beat rate. Paroxysms of supraventricular tachycardia in children are particularly severe. Symptoms of heart failure (cyanosis, tachypnoea, increased blood-filling of the lungs, hepatomegaly, vomiting) appear in about 48 to 72 hours after the onset of tachycardia with a heart beat of 180 per minute. The heart is enlarged. With all other circumstances equal, the younger the child, the more it suffers from the effects of tachycardia.

Paroxysms of tachycardia in elderly and aged patients are often complicated not only by dyspnoea and orthopnoea, but also by transitory disorders of cerebral circulation which are manifested by dizziness and disorders of vision, sometimes only in one eye. In one of our female patients with Ebstein's disease, mild hemiparesis appears during paroxysms of tachyarrhythmia and disappears a few hours after them.

Paroxysmal tachycardia and tachyarrhythmia with a clinical picture of paroxysmal dyspnoea and orthopnoea are sometimes encountered in patients with a normal heart. Orthopnoea and pulmonary oedema are often observed when tachyarrhythmia develops

in attendance to some organic heart disease. Tachyarrhythmia is a particularly common complication of the Wolff-Parkinson-White syndrome, Ebstein's disease, mitral stenosis, atherosclerotic cardiosclerosis, thyrotoxicosis and alcoholic cardiomyopathy. Transient paroxysms of cardiac fibrillation often occur in myocardial infarction, embolism of the pulmonary artery and digitalis toxicosis. With the exception of atrial septal defect, congenital heart diseases are rarely complicated by cardiac fibrillation. Cardiac fibrillation proves to be an almost invariable complication of atrial septal defect in patients after the age of 40.

Inversion of the *T* wave on the ECG is also encountered after attacks of supraventricular and especially after attacks of ventricular tachycardia. A negative *T* wave sometimes persists for four to six weeks. Paroxysms of dyspnoea or pulmonary oedema are not the only complications of paroxysmal tachycardia and ventricular tachycardia. At the same time as paroxysmal dyspnoea, pain in the region of the heart is often experienced by elderly patients and blood aminotransferase activity moderately increases.

The combination of the signs listed above brings myocardial infarction to the mind before all else as their most probable cause. The final diagnosis may be only established from the results of a more or less long-term follow-up of ECG evolution, the activity of the cardiac fraction of creatine phosphokinase or lactate dehydrogenase and the content of protein-carbohydrate complexes in the blood. Decisive importance should be attached to information on a history of recurrence of the described changes after each paroxysm of tachycardia.

Paroxysms of dyspnoea in **periarteritis nodosa** are, in all probability, of dual origin. On the one hand, patients have generalized vasculitis with high eosinophilia, and, on the other, left-ventricular failure. Attacks of paroxysmal dyspnoea may be one of the early manifestations of a disease the diagnosis of which is made on the basis of simultaneous involvement in the process of the vessels of other organs (heart, kidneys, pancreas).

Recurrent attacks of paroxysmal dyspnoea in patients with heart failure, thrombophlebitis, and parietal thromboendocarditis are usually induced by **thromboembolisms of the small branchings of the pulmonary arteries.** The development of cyanosis at the beginning of the paroxysm of dyspnoea and the appearance of signs of acute right-ventricular failure or ECG signs of acute overloading of the right ventricle are characteristic of pulmonary arterial embolism. It is particularly difficult to distinguish it clinically from the onset of myocardial infarction. Paroxysmal dyspnoea may be the first sign in both diseases. Paroxysm of dyspnoea in thromboembolism of the pulmonary artery always appears suddenly and often in full health. The attack is particularly severe at the onset of the disease

during the first few minutes. Paroxysmal dyspnoea in myocardial infarction begins less sharply. It is characteristic that dyspnoea grows gradually, developing into an attack of cardiac asthma or pulmonary oedema usually some time after the onset of the disease.

In thromboembolism of the pulmonary artery, the pulse rate is sharply increased from the very start, while arterial pressure is often reduced to a shock level. The peripheral symptoms of shock (cold limbs, profuse cold sticky sweat) are more marked at the beginning of the disease. Arterial pressure in a patient with myocardial infarction and cardiac asthma syndrome is often elevated, but may sometimes fall to a shock level in later periods of the disease. The pulse in myocardial infarction with the dyspnoea syndrome may be accelerated, though in many cases it is of normal rate or slow. Short-term cardiac fibrillation may be encountered in both diseases, but symptoms of atrioventricular block and the change of one type of arrhythmia to another are only observed in myocardial infarction.

Paroxysmal dyspnoea in myocardial infarction may be painless, although pain in the region of the heart with typical radiation is encountered more frequently during the attack. Pain never predominates in the clinical picture of pulmonary arterial thromboembolism. Chest pain arises acutely with no typical localization. Acute increase of pressure in the pulmonary artery is a constant occurrence in obstruction of one of its large branches. This leads to acute overloading and sometimes to failure of the right ventricle. Examination of a patient suffering from pulmonary arterial thromboembolism sometimes reveals cyanosis, swelling of the neck veins and pulsation in the left second and third intercostal spaces at the sternum. Intensification and splitting of the second sound over the pulmonary artery are often detected on auscultation. The sonority of the second pulmonary sound in most cases of myocardial infarction does not change.

Increased activity in the blood of creatine phosphokinase and its cardiac fraction is found three to four hours after the beginning of myocardial infarction. Their activity increases by the hour and reaches maximum by the end of the first 24 hours. In myocardial infarction echocardiography reveals akinesis, hypokinesis or paradoxical movements of the affected myocardial area and increased pulsation amplitude of the contralateral wall of the affected ventricle. No abnormalities are found on the echocardiogram in pulmonary arterial thromboembolism. Echocardiographic examination during paroxysmal dyspnoea, unfortunately, often proves to be impossible because of severe emphysema. The results of electrocardiography provide valuable diagnostic information. Though the ECG changes in acute increase of work load of the right ventricle resemble those in infarct of the posterior left-ventricular wall,

they nevertheless have some characteristic signs the proper record of which allows these two diseases to be differentiated.

Thromboembolism of the pulmonary artery is often encountered in elderly and aged patients prescribed complete bedrest and in patients of any age with initial or already manifest symptoms of heart failure. The source of the emboli in most cases are thrombophlebitis of the pelvic organs and lower limbs and parietal thrombi in the right heart cavities. Thromboembolism of the pulmonary artery has recently been found in females of child-bearing age taking oestrogenic contraceptives.

Other Diseases

Protracted and severe paroxysmal dyspnoea in middle-aged and elderly patients may be caused by **acute nephritis.** These patients experience no chest pain, as a rule. Paroxysmal dyspnoea which is easily mistaken for the painless form of myocardial infarction or hypertensive crisis predominates in the picture of the disease. Recent study of haemodynamics has shown acute left-ventricular failure to be the main cause of paroxysmal dyspnoea and pulmonary oedema in acute nephritis. Dyspnoea and congestion in the pulmonary circulation with characteristic dry and moist rales are found in the patient. In particularly severe nephritis, alveolar oedema develops in attendance to pulmonary interstitial oedema, Left-ventricular failure incident to serous inflammation of the myocardium, sharp increase in the circulating volume, and rapid elevation of arterial pressure is believed to be the principal cause of alveolar oedema.

The true cause of the paroxysm of dyspnoea is usually recognized by the attendant symptoms of acute and chronic nephritis. Thirst, oliguria, acute headache, and sometimes anuria develop simultaneously with or somewhat earlier than paroxysmal dyspnoea. Arterial pressure is elevated and the second aortic sound noticeably intensified. Characteristic changes in the urine were clearly manifest in all our cases of acute nephritis with acute left-ventricular failure. That is why in all cases of paroxysmal dyspnoea not only should the patient be asked about the volume and colour of the urine, but the urine should be examined for the content of protein, red blood cells, leucocytes and casts. The presence of oedema of the subcutaneous tissue, of the face and upper trunk makes the diagnosis noticeably easier, but often it may be absent when left-ventricular failure arises.

The ECG changes in acute nephritis are very diverse. Reduced voltage, impaired atrioventricular conduction, and the appearance of negative *T* waves sometimes in combination with an elevated *ST* segment are particularly frequent findings. Deformity of the *QRS* complex is rare. It should be emphasized that paroxysmal dyspnoea occurs at the onset of acute nephritis when the changes on the ECG are slight, as a rule. In the later stages of nephritis they are more manifest, but the diagnosis of the disease by that time already presents no difficulties.

Increase of intracerebral pressure, e.g. **after injury** or **stroke,** may be attended by pulmonary oedema the mechanism of whose development is still insufficiently known. Most patients with this type of pulmonary oedema are in a state of unconsciousness. The concomitant respiratory disorders often lead to aspiration of gastric juice into the respiratory tract, which may be one of the causes of the prolonged period of hypoxaemia. Pulmonary oedema is sometimes observed immediately or a few hours after an epileptic seizure. This type of pulmonary oedema is encountered in young persons suffering from **genuine epilepsy** and in patients with seizures associated with **extensive cerebral lesions.**

Oedema of the lungs occurring **in ascending to high altitudes** has been gaining attention in recent years. It occurs only in some individuals. It is presumably linked with hypoxia, spasm of the pulmonary veins, pulmonary circulation hypervolaemia, and other factors. Catheterization of the heart carried out in a few cases disclosed increased pressure in the pulmonary arteries and normal pressure in the pulmonary capillaries.

The clinical picture of pulmonary oedema develops 12 to 72 hours after ascending the height. The principal symptoms are as follows: cough, dyspnoea, haemoptysis, muscle weakness, unpleasant retrosternal sensations arising from time to time, cyanosis, tachycardia, a great number of sonorous moist rales in both lungs, and discharge of frothy sputum. X-ray shows a typical picture of pulmonary oedema. Small haemorrhages in the lungs and thrombi in the small branchings of the pulmonary artery are found on autopsy.

There is information in reports published in other countries about a typical clinical and X-ray picture of pulmonary oedema developing sometimes following **intravenous injection of heroin.** Oedema of the lungs is a frequent cause of death in acute heroin poisoning.

Pulmonary oedema in **sepsis** is caused by acute left-ventricular failure, increased capillary permeability, and disorders of blood coagulation.

Supplement XIX-1

Causes of Paroxysmal Dyspnoea

1. Diseases of the lungs.
   - Bronchial asthma.
   - Drug bronchospasm.
   - Parasitic pulmonary diseases.
   - Bronchopulmonary aspergillosis.
   - Broncholiths.
   - Chronic bronchitis.
   - Pneumonia.
   - Obstructive pulmonary emphysema.
   - Tracheobronchial dyskinesia.
   - Bronchial tumour.
   - Bronchoadenitis.
   - Lymphogranulomatosis.
   - Occupational diseases.
   - Foreign body in the bronchus.
   - Spontaneous pneumothorax.
   - Neurocirculatory dystonia.
   - Hysteria.
2. Diseases of the cardiovascular system.
   - Hypertensive disease.
   - Diseases of the heart muscle.
     - Myocardial infarction.
     - Aneurysm of the left ventricle.
     - Cardiosclerosis.
     - Myocarditis.
     - Cardiomyopathy.
   - Valvular heart diseases.
     - Aortic stenosis.
     - Aortic insufficiency.
     - Mitral stenosis.
     - Mitral insufficiency.
   - Bacterial endocarditis.
   - Sarcoidosis.
   - Dermatomyositis.
   - Arrhythmias.
   - Periarteritis nodosa.
   - Thromboembolism of the pulmonary artery.
3. Other diseases.
   - Acute nephritis.
   - Cerebral haemorrhage.
   - Epilepsy.
   - Heroin poisoning.
   - Sepsis.

Chapter XX

Peripheral Vasospasm

We use the term 'peripheral vasospasm' to designate three pathological conditions known as 'Raynaud's syndrome', 'livedo reticularis' and 'acrocyanosis'. Their clinical picture is explained by ischaemia of the limbs. Vasospasm is manifested most sharply in the skin vessels. In mild cases it occurs for a short time, in severer cases it is continuous only intensifying from time to time. All three clinical entities set in insidiously and patients apply for medical advice only in severe, usually far-advanced cases.

Raynaud's Disease

Periodically occurring vasospasm of the fingers was first described by M. Raynaud (1888), who considered it to be an independent disease. It was later established that typical attacks of ischaemia of the limbs may be encountered in many diseases, in view of which it became necessary to separate Raynaud's 'idiopathic' syndrome (an independent disease) from an identical syndrome of quite definite origin. In the Soviet literature the first form is known as 'Raynaud's disease' and the second as 'Raynaud's syndrome'.

The onset of Raynaud's disease is insidious. Usually the fingers are affected first: they become pale because of ischaemia caused by arrest of circulation in the affected fingers. Under the effect of vasoactive substances accumulating in the ischaemic fingers the capillaries open. The arteries of the fingers are still in a state of spasm. Oxygen from the capillary blood is consumed and the fingers turn cyanotic. Short-term episodes of vasospasm take place unnoticed. If the episode lasts longer than 30 minutes a feeling of numbness is experienced in the fingers which develops into pain. The intensity of the pain is determined by the duration of the spasm.

When the attack ends the fingers gradually turn red. This is attributed to reactive hyperaemia which first appears at the base of the fingers. Clearly demarcated red and blue spots can later be seen on the fingers; these spots may change places. In severe cases this phase of the attack may last several hours. The phase of reactive hyperaemia may be absent, in which case the attack consists only of two phases, ischaemia and cyanosis. The pulse on the radial artery is well palpated throughout the attack. If the toes are in-

volved in the attack, the pulse in the dorsal arteries of the feet and the posterior tibial artery is normal.

Sclerodactylia develops when the attacks are frequent and severe. The soft tissues of the fingers gradually atrophy and movements at the joints are restricted. The fingertips are slightly distorted and almost atrophied. The terminal phalanges resolve in some cases. The skin fuses with the underlying tissues, loses its natural folds and becomes shiny and hard. Gangrene of the fingers is a very rare occurrence, but small superficial ulcers sometimes form on the fingertips.

The described attacks of peripheral vasospasm occur both in females and in males, but incidence is five times greater in females than in males. This disease is usually found in females of childbearing age. It begins with affection of one of the fingers as a rule. With time, the episodes of vasospasm spread to all the other fingers of the hand and eventually to the fingers of the other hand. Simultaneous involvement of the toes is observed in approximately 40 per cent of the patients. In most cases the fingers are affected much earlier than the toes. Numbness of the tip of the nose, ears and tongue is noted during an episode in rare cases.

The attacks are usually precipitated by cooling, emotional stress, but sometimes there seems to be no obvious cause. The attacks become longer, more frequent and severer in the cold seasons of the year. The appearance of the limbs is absolutely normal between attacks. Increased perspiration and a decrease in skin temperature are sometimes observed. Raynaud's disease takes a progressive course in about a third of the patients. Scleradactylia develops at most in 1.6 per cent of patients.

According to contemporary standards, the diagnosis of Raynaud's disease may be made in cases in which the typical episodes occur under the effect of cold or emotion and when both upper or lower limbs are involved; the pulse in the afferent arteries must be clearly palpated even during the attack. Small skin ulcers may form on the distal phalanges, but not gangrene of the fingers. All diseases which can be complicated by Raynaud's syndrome (Supplement XX-1) must be ruled out. Particular care must be taken to rule out diffuse diseases of the connective tissue. Raynaud's syndrome may be their first clinical manifestation. It sometimes develops several years before the other signs of these diseases appear.

Raynaud's Syndrome

Occupational Raynaud's syndrome. Periodical vasospasm of the fingers or hands ('spastic anaemia of the hands') often develops in individuals handling vibrating pneumatic tools. A special study of this problem showed that the most intensive vasospasm develops

in a person using a tool vibrating at a rate of 125 Hz. The main role in the development of vasospasm may probably be attributed not to vibration alone, but to the combination of its effect with cooling of the hands and long-term tension of their muscles holding the pneumatic hammer, pneumatic drill-bit, diesel saw or any other vibrating tool. Much importance is also attached to whole body cooling, evidence of which is the sharp decrease in the number of attacks during the warm seasons (Supplement XX-2).

Vasospasm may occur from time to time in persons whose fingertips or the whole hand suffer minor traumas during work (pianists, typists, drillers, tool-grinders, some categories of mechanics and workers on sewing machines). In some patients plethysmography and arteriography demonstrated signs of marked spasm of the vessels of the hand occurring during work. It is quite possible that the vasospasm develops under the effect of neuritis induced by vibration. Raynaud's syndrome of occupational origin is unilateral as a rule. This unilateral affection sometimes takes a progressive course and leads to the formation of small superficial ulcers usually in the skin folds of the fingers. Vasospasm develops in most patients with Raynaud's disease and in those with occupational Raynaud's syndrome when the affected limb is held in cold water.

Organic lesion of the limb arteries. As it is pointed out above, Raynaud's disease is usually encountered in females. Peripheral vasospasm in males is of secondary origin in most cases. Its underlying factor may be either *stenosing atherosclerosis* or *thromboangiitis obliterans.* These diseases closely resemble each other in their clinical manifestations but atherosclerosis usually begins after the age of 50, while obliterating thromboangiitis sets in before the age of 30.

The arteries of the lower limbs are most frequently affected. Intermittent claudication is the first sign of vascular insufficiency. It is later joined by pain in the limbs experienced at night when the patient is in bed. The pulse in the arteries of the involved limb is weak, or even absent. The feet are cold. In thromboangiitis obliterans both limbs are usually affected but one is affected more than the other. In far-advanced cases the arteries of the upper limbs are also involved. In very rare cases the disease begins with affection of the upper limbs.

In thromboangiitis obliterans the attacks of vasospasm are usually induced by cooling and spread only to one or two fingers. Only the first phase, blanching, occurs. The attacks of peripheral vasospasm sometimes develop before the other signs of thromboangiitis. In such cases it is very difficult to differentiate them from Raynaud's disease.

Pathological and angiographic examination revealed that thromboangiitis was often misdiagnosed in the past as segmental athero-

sclerosis of the lower limbs. The concept of thromboangiitis obliterans as a clinical entity has now regained its popularity. Its diagnosis may be considered substantiated if a lesion of the upper limb arteries is proved in a patient with migrating thrombophlebitis and if the patient experiences episodes of vasospasm in only one or two fingers of one hand. Raynaud's syndrome is encountered more frequently than the absence or sharp diminution of the pulse on the radial and ulnar arteries in thromboangiitis obliterans of the upper limbs.

Raynaud's syndrome often develops in disorders of normal blood flow in the subclavian arteries. These disorders are most commonly induced by atherosclerotic patches and inflammatory processes in the orifices of arteries arising from the aortic arch, by thrombosis, embolism, and often by aneurysms of the upper limb arteries. Congenital anomalies of the ribs and the scalenus muscle and diseases leading to compression of the vascular bundle of the upper limbs are also sometimes complicated by Raynaud's syndrome.

Accessory cervical ribs are discovered in approximately 0.5 per cent of persons who are examined and are often combined with anomaly of the first rib and a subclavian artery arising at a higher level than normal. In about 10 per cent of patients with a cervical rib, the elongated subclavian artery is usually compressed at the point where it passes through the scalenus muscles and is sometimes also thrombosed. The postcompression part of the artery is usually dilated. The branchial plexus is compressed together with the subclavian artery.

The clinical manifestations of the *cervical rib syndrome* may be separated into vascular and neural. The neural signs are observed more frequently and are more conspicuous than the symptoms of involvement of the vascular system. The sensation of pain may be brief or continuous. The pain may be mild or only felt as pricking or numbness in the hand. It may also be sharp. In graver cases continuous pain is felt in the neck and is referred to the arm, forearm and sometimes to the hand of the limb involved. It intensifies markedly when the limb is abducted or raised. Painters, mechanics and persons employed in other jobs requiring them to make such movements very often are sometimes obliged to change their occupation because of severe pain.

Arterial pressure and pulse on the involved limb may be normal at rest. To reveal an unequal pulse the patient is asked to be seated, to strain himself, and then turn his head first to the side of the lesion, and then to the contralateral side. During the test the pulse on the side of the lesion diminishes or completely disappears and sometimes pain appears in the neck and is referred to the arm or forearm. In severe cases a continuous murmur is audible in the supraclavicular fossa of the affected side. The fingers on this side

are cold all the time or the vasospasms occur from time to time. Trophic changes sometimes develop in the nails and small superficial ulcers may form. Gangrene of the fingertips may develop in thrombosis of the subclavian artery.

The *scalenus syndrome* develops as a consequence of compression of the subclavian artery and vein or the brachial plexus as they pass between the scalenus muscles. In severer cases hypertrophy of the anterior scalenus muscle and its fibrosis or thrombosis of the subclavian vein is found. The scalenus syndrome (just as the cervical rib syndrome) is manifested by periodical vasospasms of the fingers on the side of the lesion. Numbness and pain in the hand are markedly intensified in abduction of the limb and when shouldering a load and typing for a long time.

Compression of the brachial plexus is displayed by abnormalities on the electromyogram. Impaired excitability and conduction of the muscle in the scalenus syndrome are detected before the development of thrombosis of the subclavian vessels. The scalenus syndrome must be differentiated from cervical osteochondrosis and tumour of the cervical segment of the spinal cord which are marked not only by vasomotor disorders but by disorders of the activity of the sensory and motor neurons.

Diffuse diseases of the connective tissue usually begin with affection of one organ or one functional system. This monosyndromal period of the disease may last months or years. Its clinical manifestations become severer with time. In the period of generalization of the process, the disease becomes polysyndromal which noticeably eases its identification. Raynaud's syndrome is often the only manifestation of scleroderma and systemic lupus erythematosus. It is also often observed in other collagenoses in the period of generalization of the process.

Systemic lupus erythematosus commonly begins with skin and joint lesions. Raynaud's syndrome is found in 10 to 35 per cent of cases of this disease and may be its only clinical sign for six to ten years (Nasonova, 1972). This specific feature of the disease is delicately formulated in the rule to the effect that any form of Raynaud's syndrome in girls and young women should be regarded a manifestation of systemic lupus erythematosus until it becomes possible to reject this diagnosis.

The attacks of peripheral vasospasms in systemic lupus erythematosus are at first mild and short in duration, but with time grow in severity. They begin appearing even in the slightest cooling and last hours. Fever and affection of the joints appear in attendance to Raynaud's syndrome with time and anaemia, hepatosplenomegaly and hypergammaglobulinaemia develop. The monosyndromal disease turns into a polysyndromal form. A large number of lupus cells appear in the blood. The episodes of peripheral vasospasms

grow in severity and may terminate in capillaritis or even gangrene of the fingers.

Scleroderma like systemic lupus erythematosus is encountered much more frequently among females than among males. Raynaud's syndrome develops in 80 to 90 per cent of patients with scleroderma, in a third of whom it remains the only clinical manifestation of the disease for several years. The affection is always bilateral. Marked hypersensitivity of these patients to cold is one of the earliest signs of the disease. The fingers react particularly sharply to cooling. They turn cold and white even at room temperature. This is explained by the sharply diminished blood flow in the finger pads, which in patients with scleroderma is half that in healthy persons (Coffman, 1970). In the late stages of the disease, the fingers covered by thick shiny skin become immobile and are usually in a state of more or less marked flexion contracture. Peripheral vasospasm may be transient or continuous with periodical intensification. The spasm in the vessels of the thumb is characteristically less marked than the spasm in the vessels of the other fingers. Angiography of the upper limb arteries disclosed the cause of this. It was found that in patients with scleroderma stenosis of the ulnar artery always sets in a little earlier and is sharper than stenosis of the radial artery. The ulnar artery is often thrombosed when the radial artery is still unobstructed.

The forms of scleroderma beginning with peripheral vasospasms differ from other forms in following a more favourable course. The disease prevails among females. The periodical vasospasm on the limbs is soon replaced by a continuous spasm. Changes in the skin with oedema of the subcutaneous tissue are mainly localized on the limbs and face. These are soon joined by inexplicable loss of body weight, shedding of hair and later by disturbances in the function of one of the internal organs, most commonly the oesophagus, heart or lungs. Hyperproteinaemia and hypergammaglobulinaemia are usually detected in this stage of the disease. With the appearance of pigmented spots on the skin and atrophy of the muscles, the diagnosis of scleroderma becomes obvious.

Rheumatoid arthritis is often complicated by marked disorders of peripheral circulation induced by the simultaneous or separate action of two mechanisms, namely, peripheral vasospasms and disturbances in the blood rheological properties. The prevalence of Raynaud's syndrome with its characteristic vasospasms developing in response to cooling or emotional stress is quite obvious in some cases. In others the cooling is attended by the formation of stases and thrombi in the small vessels of the limbs. The activity of this mechanism leads to the development of small necroses which eventually turn into small ulcers.

Arteriography established that peripheral vasospasm in rheuma-

toid arthritis occurs only in patients with occlusion of one or more digital arteries. On the basis of this it can be stated that the vascular factor is much more important than the rheological factor in the origin of the peripheral vasospasm.

Raynaud's syndrome is often observed in some period of dermatomyositis. It is a far less frequent occurrence in arteritis nodosa and primary pulmonary hypertension.

Other causes. Short-term peripheral vasospasm and continuous vasospasm intensifying from time to time are sometimes encountered in patients suffering from *polycythaemia*, *myeloma*, *lymphogranulomatosis*, *lymphoid leukaemia*, *Waldenström's macroglobulinaemia* and some other diseases marked by impaired rheological properties of the blood. In these diseases peripheral vasospasm develops as a rule when the environmental temperature drops. The cooling is evidently attended by intravascular coagulation of the plasma protein. The obstruction of the small vessels occurring for some period of time in this case may lead to thrombosis and the formation of trophic ulcers on the skin.

Tumours arising from the lymphocytes and plasma cells are characterized by intensified production of monoclonal immunoglobulin molecules and their fragments which noticeably change the physico-chemical properties of the blood. Blood viscosity increases particularly sharply when immunoglobulins A accumulate in the blood since they show a tendency to polymerization. When the temperature drops immunoglobulins M and G are converted to a jelly-like state or they undergo reversible precipitation. Raynaud's syndrome is one of the consequences of the accumulation of these immunoglobulins (commonly known as cryoglobulins) in the blood. It may be that vasoactive peptides contributing to the development of peripheral vasospasms accumulate in the blood simultaneously with the cryoglobulins.

Cryoglobulins, cold agglutinins and increased blood viscosity may be presumed to be the causes of Raynaud's syndrome only in patients with no abnormalities in the large arteries.

Symmetric gangrene of the limbs was observed in the past in poisoning with ergot. *Ergot preparations* possessing a direct vasoconstrictive effect are widely used now in the treatment of migraine. Their abuse sometimes causes the development of Raynaud's syndrome. Peripheral vasospasm develops in approximately 7 per cent of patients who take methysergide, a serotonin antagonist, to relieve migraine and in most patients who take methylamphetamine for a long time in the treatment of obesity. The mechanism of their effect is unknown. The assumption that they potentiate the action of catecholamines is not always fully convincing, because vasospasm sometimes occurs after the intake of very small doses.

Raynaud's syndrome or continuous spasm of the digital arteries occurs abruptly in the use of these preparations. The arteries of the lower limbs are often involved in the process and intermittent

claudication develops. Arteriography demonstrates a sharp spasm of the main arteries or even the cessation of circulation in them, while collateral circulation is maintained. The condition proved to be reversible when the drug causing it was discontinued before the formation of the thrombus.

Raynaud's syndrome is sometimes encountered in poisoning by arsenic and heavy metals. Sometimes it develops in workers employed in the production of vinyl chloride.

Livedo Reticularis

The term 'livedo reticularis' (reticular purplish mottling of the skin) is used to designate a condition of the skin when a pattern resembling lace or a fishing net is seen on its surface. The pale centre of each mesh of this net is caused by spasm of the perpendicular arteriole perforating the dermis. The cyanotic periphery of each pale skin area is caused by congestion of the reduced blood in the venous plexuses attendant to the arteriole. Girls and young women usually suffer from this disease.

In mild cases the skin of the lower limb takes on a marble-like appearance when the environmental temperature drops, but becomes normal soon after the patient returns to a warm room. In severer cases the mottled or mesh-like pattern of the skin becomes permanent; mottling of the skin intensifies noticeably on cooling, diminishes in a warm room, but does not disappear completely. The changes in the skin are most vivid on the thighs. Small ulcers form there in rare cases. The cause of the arterial spasm is not known. The prognosis is quite favourable if livedo reticularis is the only disease. Carriers of this disease suffer only from their unpleasant appearance throughout life.

In some cases livedo reticularis proves to be the first clinical manifestation of some generalized disease, such as diffuse diseases of the connective tissue, diseases of the endocrine glands, malignant gammapathies, polycythaemia, drug intolerance and diseases of the nervous system. Livedo reticularis and Raynaud's syndrome are often encountered in one and the same patient.

Acrocyanosis

Acrocyanosis is manifested as an irregular dark purple colour of the fingers and toes. The discoloration may sometimes spread to the hands and feet and very rarely to the legs, cheeks and chin. The cyanotic limbs are usually covered with cold sweat. The cyanosis usually disappears in a warm room, but intensifies under the effect

of cooling and excitement. The disease is sometimes of familial character. In our practice we encountered it in two generations of one family.

Acrocyanosis must be differentiated from Raynaud's syndrome and from diffuse cyanosis. Cyanosis of the fingers and toes develops from time to time in Raynaud's syndrome but is permanent in acrocyanosis. It differs from diffuse cyanosis by a normal content of oxygen in the arterial blood and affection of just the hands and feet.

Raynaud's syndrome is diagnosed when the patient describes the episodes of short-term vasospasms of his fingers and toes and when the physician himself witnesses at least one such vasospasm. It should be borne in mind that attempts to reproduce peripheral vasospasm by cooling the limbs in cold water, for instance, often fail. It is also quite easy to make the diagnosis of permanent vasospasm manifested as livedo reticularis or acrocyanosis. It is far more difficult to identify the cause of these syndromes. Their aetiology sometimes becomes obvious only after observing the patient for many years.

Supplement XX-1

Causes of Peripheral Vasospasm

1. Raynaud's disease.
2. Raynaud's syndrome.
   - Occupational spastic anaemia of the hands.
   - Organic lesion of the limb arteries.
   - Diffuse diseases of the connective tissue.
   - Other causes.
3. Livedo reticularis.
4. Acrocyanosis.

Supplement XX-2

Causes of Raynaud's Syndrome

1. Injury (traumatic vasospasm).
2. Diseases of the limb arteries.
   - Stenosing atherosclerosis or arteritis.
   - Buerger's thromboangiitis obliterans.
   - Arterial embolism.
3. Diffuse diseases of the connective tissue.
   - Scleroderma.
   - Systemic lupus erythematosus.
   - Rheumatoid arthritis.
   - Dermatomyositis.

4. Diseases of the nervous system.
   Poliomyelitis.
   Stroke.
5. Syndrome of the upper cervical aperture.
   Cervical rib syndrome.
   Scalenus syndrome.
   Costoclavicular syndrome.
6. Increased blood viscosity syndrome.
7. Poisoning with ergot preparations, methylamphetamines, etc.

Chapter XXI

Pleurisy

Fluid accumulates in the pleural cavity either as a consequence of affection of the pleura lining it or in association with general disorders of water-electrolyte metabolism in the body. The former happens in inflammation of the pleura induced by the causative agents of infectious diseases, in involvement of the pleura in neoplastic processes, and in its infiltration by lymphoid or myeloid tissue; while the latter is often encountered in injury, scurvy, in diseases complicated by heart failure or the nephrotic syndrome, and in some other diseases (see Supplement XXI-1).

The differential diagnosis in cases with accumulation of fluid in the pleural cavity may be subdivided into two stages. First the syndrome is identified, i.e. distinguished from other syndromes with similar clinical signs, after which its cause is determined.

Identification of the Pleural Effusion Syndrome

The physical signs of fluid accumulation in the pleural cavity are commonly known. When there is much fluid in the pleural cavity, percussion along the posterior surface of the chest reveals three zones according to the acoustic properties. A clear pulmonary resonance is elicited over the lung apex and a dull note over its base. There is a zone of tympany between them. Tympany is caused by partial atelectasis of the lung which had lost its tension to a great measure.

Vocal fremitus over the zone of the dull percussion note is either diminished or not produced at all. The respiratory murmurs over the zone of absolute flatness are not heard or are diminished. Diminished bronchial respiration is heard as a rule over the zone of tympany. Vesicular respiration is heard over the zone of the resonant pulmonary sound.

Despite the great number of guiding signs the diagnosis of the pleural effusion syndrome often gives rise to doubts most of which are dispersed after X-ray examination. A diagnostic test for the functioning of the pleural cavity is best carried out after the X-ray

examination. It verifies the presence of fluid in the cavity and helps in determining its character. Additional examination most often has to be resorted to in distinguishing the pleural effusion syndrome from pneumonia, tumour of the lungs, and some other diseases and syndromes listed in Supplement XXI-2.

Lobar or **confluent lobular pneumonia** is sometimes misdiagnosed as accumulation of fluid in the pleural cavity. This error is easily made at the bedside of a patient with pneumonia developing in attendance to influenza. The severe affection of the bronchial mucous membrane in influenza and some other infectious diseases of the lungs leads in some cases to almost total obstruction of the bronchus draining the involved pulmonary segment. As a result of this, the percussion note over the diseased segment or lobe of the lung becomes dull and respiration sharply diminishes. In some instances the respiratory sounds are not heard at all for some time.

The correct diagnosis is made if the borders of the dullness are taken into account. The zone of the dull percussion note in pneumonia coincides with the projection of the pulmonary lobe and lobes on the chest surface. In pleural effusion, the upper border of the dullness forms Damoiseau's line whose upper convexity is on the axillary line. We were convinced, time and again, of the value of determining Garland's and Rauchfuss' triangles. Simultaneous determination of the zones of dull and resonant pulmonary percussion notes and tympany as well as the corresponding zone of diminished respiration and respiration with a bronchial tinge helps greatly in the differential diagnosis between pneumonia and pleural effusion.

The collection of fluid in the pleural cavity is sometimes mistaken for pneumonia. This happens when bronchial respiration is heard over the area of absolute flatness. This is often encountered in children with extensive effusion completely compressing the lung. The heart in such cases is displaced to the healthy side. It is known that the heart is not displaced in pneumonia. Cough may occur in both diseases, it is attended by expectoration in pneumonia, but is dry in pleural effusion. The differential diagnosis is made much easier if other extrapulmonary signs of the disease are analysed, such as the character of fever, the degree of leucocytosis, and the order in which some of the signs of the disease appear. Comparison of the X-ray findings with these signs allows the correct diagnosis of this syndrome to be made.

Extensive adhesions dull the percussion note and produce a shadow on the radiograph. It is at times hard to distinguish these signs from similar signs in pleural effusion. The normal respiratory excursions of the diaphragm are also often restricted because of the adhesions. The syndromes differ in the character of heart displacement. In extensive effusions the heart is displaced to the healthy

side of the chest, whereas in large pleural adhesions it is displaced to the involved side. Moreover, in adhesions the respiratory murmurs are clearly audible despite the dullness, whereas in pleural effusion they are noticeably diminished. The zone of tympany is found only in the pleural effusion syndrome.

A rather dull percussion note and diminished respiration are always heard over the **zone of atelectasis** developing in association with stenosis or obstruction of the bronchus by a tumour. The mediastinal organs are displaced to the involved side in atelectasis and to the contralateral side in pleural effusion. X-ray examination demonstrates signs of bronchial obstruction long before the physical signs of atelectasis appear. In our practice we encountered large *mediastinal tumours* which compressed the upper lobe and, causing its atelectasis, led to the appearance of a dull percussion note and diminished respiratory murmur. Combination of these signs is observed in large *pulmonary tumours*. A dull percussion note and the absence of the respiratory sound are constant signs of fibrothorax.

Upward displacement of the diaphragm is marked by a diminished respiratory sound and a dull percussion note over the lower pulmonary lobe. Marked unilateral elevation of the diaphragm is always observed in paresis of the phrenic nerve, primary carcinoma of the liver, abscesses of the liver, subdiaphragmatic abscess, and considerable distension of the stomach, e.g. in pyloric stenosis. Bilateral upward displacement of the diaphragm is a characteristic sign of obesity and severe meteorism. Effusion in the pleural cavity and an elevated diaphragm cannot be distinguished by the results of physical examination, but are easily differentiated by X-ray of the lungs.

Hydatid disease is found in some regions of the Soviet Union. A **hydatid cyst** of the chest is mostly localized in the lower pulmonary lobe. Its favoured site is the posterior part of the right lower pulmonary lobe. A cyst adjoining the chest wall, diaphragm or the bronchial tree is sometimes flattened. The percussion note over the cyst is always dull, while respiration is either inaudible or drastically diminished. X-ray examination usually demonstrates a characteristic spherical cyst often with foci of calcification. Puncture of the cyst is contraindicated because dissemination of the cyst in the pleural cavity and lungs may occur.

The presence of fluid in the pleural cavity should be accepted as an indication for thoracocentesis which is the most reliable method for identifying the aetiology of the syndrome. The pleural fluid is either a transudate or an exudate. A transudate is fluid accumulating in the pleural cavity in generalized disorders of water-electrolyte metabolism in the body and is not a consequence of pleural inflammation. **Transudate** occurs in cirrhosis of the liver, beriberi (vitamin B_1 deficiency), hypoproteinaemia caused by starva-

tion or increased loss of protein through the gastro-intestinal tract, in heart failure, the nephrotic syndrome and severe anaemia. Each of these syndromes doubtlessly has its own causes without the identification of which its aetiological diagnosis cannot be made. It should be particularly emphasized that collection of transudate in the pleural cavity may be the only sign of latent heart or renal failure.

Inflammatory conditions of the pleura are attended by the formation of an **exudate** which may be serous, haemorrhagic, purulent or chylous. In following this traditional division it must be borne in mind that haemorrhagic exudate differs from serous exudate only in the colour of the fluid and that in most cases a chylous fluid accumulates in the pleural cavity in no association with inflammation of its pleural lining. The accumulation of exudate is sometimes the only sign of the disease. Such an isolated exudate may be distinguished from an isolated transudate in appearance, relative density, and protein content.

An exudate is always opalescent and clots on standing; its relative density is more than 1018, while the protein content exceeds 30 g/l, often being as high as 50 g/l. A transudate is clear and does not clot on standing. Its relative density is below 1015, while the protein content usually ranges from 5 to 15 g/l. In practice, the intermediate values are explained by the coexistence of two processes, for instance, fluid transudation into the pleural cavity and inflammation of the pleura, as it often happens in pulmonary infarction in a patient with heart failure. The cytological composition of the exudate, the number of neutrophils, white and red cells, cells of the mesothelium and tumour cells are also of definite diagnostic value.

Causes of Pleural Effusion

Fluid accumulates in the pleural cavity as the result of either increased permeability of the vessels or mechanical impairment of their intactness. Increased permeability of the pleural vessels leads to the formation of a transudate. Inflammatory lesions of the pleura are marked by the formation of an exudate. According to the content of formed blood elements, serous, haemorrhagic and purulent exudates are distinguished.

A haemorrhagic exudate is one in which each millilitre contains more than 5000 red blood cells. An exudate is considered purulent if each millilitre contains more than 10 000 leucocytes. The exudate is called serous when the content of formed blood elements is below these values. As it is shown in Supplement XXI-2 serous and haemorrhagic exudates often develop in one and the same disease.

Mechanical ruptures of the pleural blood vessels lead to **haemothorax,** i.e. the accumulation of blood in the pleural cavity. In our times haemothorax most frequently proves to be a complication of *surgical operations* carried out in the chest.

With the exception of chest injury the only causes of haemothorax are rupture of an *aneurysm of the aorta* into the pleural cavity and tearing of vacularized pleural adhesions during the formation of spontaneous pneumothorax.

Spontaneous pneumothorax is encountered most frequently among males of 20 to 40 years of age. The right side is involved much more frequently than the left. After escaping into the pleural cavity, the air rises to the lung apex. An exudate or blood accumulating in the pleural cavity collects in its lower half producing a horizontal level clearly demonstrated by X-ray. Chest pain and attacks of dyspnoea are the first signs of spontaneous pneumothorax. They occur simultaneously or separately. Dyspnoea is very severe as a rule at the moment when pneumothorax occurs. In cases of non-valvular pneumothorax, it diminishes noticeably or disappears in 24 hours.

The formation of a dissecting aneurysm of the aorta is marked by excruciating pain mostly in the back. Another characteristic feature is radiation of the pain along the course of the aorta and its branches, i.e. on the lateral surfaces of the chest, the abdomen and the lower limbs. A dissecting aneurysm of the descending aorta adjoining the left lung ruptures mostly into the pleural cavity. Bleeding from this aneurysm occurs into the left pleural cavity, posterior mediastinum or left lung. The clinical picture of dissecting aortic aneurysm comprises the pain syndrome which is always much sharper than the pain syndrome in spontaneous pneumothorax, gradually increasing dyspnoea caused by the mounting pressure exerted on the lung by blood escaping into the pleural cavity, and rapidly growing anaemia. Air does not appear in the pleural cavity in this case. The spread of haematoma from the mediastinum to the base of the neck is sometimes observed.

The term **'chylothorax'** designates the accumulation of chylous or pseudochylous fluid in the pleural cavity. The chylous fluid enters the pleural cavity from the chyliferous vessels, but most often from the ruptured thoracic duct. It is rich in neutral fat and fatty acids, and therefore stains well with Sudan III. It contains very little cholesterol. The pseudochylous fluid forms under the effect of fatty degeneration of malignant cells. It is rich in cholesterol and lecithin and contains only a small amount of neutral fat. It is similar to chylous fluid in colour but is easily distinguished from it when stained with Sudan III.

Injury is the most common cause of chylothorax. In most cases chylous fluid accumulates in the pleural cavity five to seven days

after the injury or operative intervention. Within this period the chylous fluid flows from the ruptured vessel into the mediastinum from which it usually enters the left pleural cavity. The acute respiratory insufficiency syndrome develops at this moment. The non-traumatic causes of chylothorax are as follows (in diminishing succession of incidence): *carcinoma of the bronchus* and its metastases, *tuberculosis* of the lymph nodes with compression of the thoracic duct, retroperitoneal *tumours* of the type of lymphogranulomatosis and haematosarcoma, and parasitic affections of the lymph vessels among which *schistosomiasis* and *filariasis* are prevalent. In about one third of cases the cause of chylothorax remains unknown.

Hydrothorax (transudate in the pleural cavity) is encountered in many diseases marked by increased hydrostatic pressure in the veins of systemic and pulmonary circulation, in hypoproteinaemias and in any generalized increase in vascular permeability. Hydrothorax is a particularly regular occurrence in *heart diseases* complicated by circulatory failure, in *diseases of the pericardium* (constrictive pericarditis), the *nephrotic syndrome*, *hypoproteinaemias* consequent upon starvation or increased protein loss through the gastrointestinal tract, *scurvy* and *lack of vitamin* B_1 (beri-beri). Hydrothorax occurring in the mentioned generalized disorders of water-electrolyte metabolism and in generalized disorders of capillary permeability is mostly localized in the right pleural cavity. In severe cases it develops in both pleural cavities.

Predominant involvement of the right pleural cavity is also noted in many other diseases. In our practice we had patients with mitral stenosis and cirrhosis of the liver in whom the transudate developed and persisted in the right pleural cavity two or three years before the appearance of ascites. In cirrhosis, hydrothorax on the left side and bilateral hydrothorax are encountered much more frequently than hydrothorax on the right side.

In 1937 Meigs and Cass described seven cases of ovarian fibroma with ascites and hydrothorax, i.e. *Meigs' syndrome*. It has been established that not only fibromas but many malignant and other benign tumours of the ovaries are complicated by ascites and hydrothorax in 2 or 3 per cent of cases. The fluid collects in the right pleural cavity as a rule. Removal of the ovarian tumour, benign or malignant, always leads to the disappearance of both ascites and hydrothorax. Evidently the development of ascites and hydrothorax in tumours of the true pelvis is not associated with metastasis of the tumour and cannot be accepted as signs of a hopeless prognosis. It has also been described in carcinoma of the pancreas and retroperitoneal lymphosarcoma.

Peritoneal dialysis has been widely used in the last decade for the control of renal insufficiency and correction of impaired blood

water-electrolyte composition. In approximately 6 per cent of cases the procedure is complicated by hydrothorax. It has been suggested that the fluid enters the pleural cavity by way of the lymphatic vessels penetrating the diaphragm. Fluid characteristically accumulates in the right pleural cavity four times as frequently as in the left pleural cavity.

Myxoedema is often complicated by the accumulation of fluid in the pericardial cavity. It proves to be hydropericarditis in most cases. In our practice, we encountered simultaneous collection of fluid in the pericardium and in the pleural cavities. Myxoedema with isolated hydrothorax has been described.

The content of protein in these cases of hydrothorax is not constantly low. In some cases of heart failure, myxoedema, cirrhosis of the liver and other diseases the protein content in the pleural fluid may vary from 25 to 30 g/l. This fluid may evidently be considered a transudate or exudate.

Purulent pleurisy (empyema of the pleura) is always a complication of some other chronic disease. In the internist's practice, the most common cause of purulent pleurisy is *bacterial pneumonia*, pneumococcal pneumonia in particular. This is possibly explained by the character of a given contingent of patients. Pneumococcal pneumonia still predominates in the departments for internal diseases in the large city hospitals. Virus pneumonia is not complicated by empyema. During epidemics of influenza, empyema is caused by an attendant bacterial infection and not by influenza virus.

The clinical picture of purulent pleurisy is always severe. It comprises high fever of irregular type with recurrent chills and sweating, severe toxicosis, and rapid loss in body weight and strength. High leucocytosis with a shift to the left (often to the presence of myelocytes) and rapid development of progressive hypochromic anaemia are characteristic signs. ESR may be as high as 40-60 mm/hour.

In our practice, empyema developed in pneumococcal and streptococcal pneumonias either in the acute period or soon after the disease had ended. The occurrence of empyema is most probable in those cases of pneumonia in which full doses of an adequate antibiotic lead only to a brief fall in body temperature. A flat percussion note and bronchial respiration are heard over the involved pulmonary lobe and over the base of the lungs. The results of physical examination of these patients create the impression that the resolution of pneumonia is delayed in the stage of bronchial respiration. Leucocytosis is high. The final diagnosis is established from the results of thoracocentesis. The diaphragm on the involved side is noticeably elevated and puncture of the pleural cavity should therefore be made about 1 or 2 cm below the upper limit of the dullness.

Empyema may develop in attendance to *pulmonary suppuration* (suppuration of a pulmonary cyst, abscess or gangrene of the lung). The diagnosis is based on the same signs from which the diagnosis of postpneumonic empyema is established. The pleural exudate in such cases has a putrid odour. If empyema is caused by anaerobic bacteria, culture of the pleural exudate will be sterile because it is usually inoculated on aerobic medium. Melting of the pulmonary tissue sometimes results in rupture of the abscess into the pleural cavity. A communication is thus established between the cavity of the abscess and the pleural cavity through the pleurobronchial fistula formed in this manner. Pyopneumothorax forms, the diagnosis of which is made from the appearance of air and a horizontal fluid level in the pleural cavity.

Tuberculosis of the lungs is sometimes complicated by empyema because caseous foci melt and penetrate the pleural cavity. A pure culture of *Mycobacterium tuberculosis* is often identified in the pus. Empyema was a common complication of artificial pneumothorax in the past. Now spontaneous pneumothorax in active pulmonary tuberculosis is the most frequent cause of tuberculous empyema. In some cases, tuberculous empyema may persist years without giving rise to any particular complaints, in others it takes the course of an acute disease with high fever and severe toxicosis. Just as in empyema of other origin, the pus in tuberculous empyema may cause melting of the pulmonary tissue and enter the bronchus with the formation of a bronchial fistula. This is clinically manifested by copious purulent expectorations in coughing. The diagnosis of tuberculous empyema is of vast practical significance because the disease calls for specific methods of treatment.

Carcinoma of the bronchus is often complicated by pneumonia in the atelectatic segment of the lung. This pneumonia (like any other) may be complicated by empyema. In some cases, empyema develops as a complication of traumatic haemothorax. This happens mostly in penetrating chest injuries. In some cases of septicopyaemia, the lungs prove to be the sites of septic emboli. Bilateral empyema may develop in such instances.

Subdiaphragmatic abscesses are mostly attended by serous pleurisy, though empyema may also develop in cases of particularly virulent infection. *Abscesses of the liver* occurring as a complication of amoebiasis, purulent cholecystitis or surgery of the abdominal cavity may also lead to empyema of the right pleural cavity. In rare cases, pleural empyema develops as a complication of pulmonary ecchinococcosis or as a manifestation of actinomycosis.

Acute pneumonia may be complicated by empyema and by abscesses of the lungs. The correct diagnosis of these complications is of immense practical importance because it allows the physician to refrain from performing paracentesis and in this way to prevent

infection of the pleural cavity. Abscess of the lung is easily differentiated from pleurisy with effusion by X-ray. Cough with expectoration of foul-smelling sputum is often observed in pulmonary abscess but never in pleural empyema. The characteristic changes in the findings of percussion and auscultation described above occur only in empyema of the pleura. They never happen in abscess of the lung.

A subdiaphragmatic abscess is always marked by considerable upward displacement of the diaphragm and effusion into the pleural cavity on the involved side. The findings of physical examination in such cases may be no different from those in pleurisy with effusion. Pus can be collected from a subdiaphragmatic abscess if the pleural cavity is punctured not close to the upper boundary of the dullness, but at a lower level. These two diseases differ sharply in the medical history and the condition of the abdominal cavity. As it is pointed out above, subdiaphragmatic abscess is always a second disease. It occurs as a complication of appendicitis, abscess of the liver, pyelophlebitis, cholecystitis, peritonitis or covered perforation of some hollow abdominal organ. Pulmonary empyema is a complication of pneumonia or infectious diseases mainly with involvement of the thoracic organs.

Non-suppurated effusions are divided into serous, serohaemorrhagic and haemorrhagic. Purely haemorrhagic effusions are encountered most frequently in scurvy, tuberculosis, and carcinoma or mesothelioma of the pleura. Serous effusions occur in most of the other diseases. Repeated puncture in one and the same patient sometimes shows that a serous effusion transforms into a haemorrhagic, or a haemorrhagic effusion to a serous effusion. A change in the red cell count in the effusion is of no importance in making the differential diagnosis. The cause of the effusion is identified much easier if the number of lymphocytes in it is counted or the rate of its accumulation after thoracocentesis is determined. The effusion collects particularly rapidly in tuberculosis or tumour of the pleura, in non-obstructive thrombosis of the pulmonary artery, and in all diseases marked by atelectasis of the lungs.

Tuberculosis is still the most common cause of *pleurisy with effusion* in adults. In about three fourths of cases the disease begins suddenly and resembles acute lobar pneumonia in the first days (sudden pain in the side and continuous fever reaching to a level of 39°C). General weakness is sometimes just as severe as in pneumonia, but at other times the patient's general condition hardly changes: despite the high temperature, he is ambulant and can visit the doctor unassisted and describe his ailment in detail. Acute lobar pneumonia always begins with a chill. The other differential diagnostic signs of pleurisy with effusion and pneumonia are mentioned above. The onset of pleurisy with effusion may be acute, but with

no shaking chills. Much less frequently pleurisy with effusion of tuberculous aetiology sets in insidiously. There are subfebrile body temperature, rapid fatiguability, mild pleural pain, dry cough and loss of body weight. Pleurisy with effusion may be the only manifestation of tuberculosis but usually it is found when there are foci in the lungs. The pleural fluid may be haemorrhagic, but in most cases it is straw-coloured: it is clear and has a high protein content. The lymphocyte content in the effusion is characteristically high. Lymphocytes may account for 70 per cent of the cell composition of the effusion in the late stages of the disease.

Neutrophils are often found in the effusion in the early stages of the disease and sometimes constitute 20 to 30 per cent of its cell composition. A higher neutrophil count in tuberculous effusions is not encountered.

Involvement of only one pleural cavity, a high lymphocyte content in the pleural effusion and a positive Pirquet's or Mantoux test are considered characteristic signs of tuberculous pleurisy. Their presence suggests the tuberculous aetiology of pleurisy with effusion. Moreover, a negative result of the tuberculin test practically rules out the diagnosis of tuberculous pleurisy. Nevertheless, strictly speaking, these criteria provide grounds only for presuming the tuberculous aetiology of the pleurisy. The final diagnosis may be established only after isolation of *Mycobacterium tuberculosis* from the effusion and after the discovery of characteristic granulomas in pleural biopsy.

Pleurisy with effusion as a complication of *bacterial pneumonia* is encountered at any age. Virus pneumonia is very rarely complicated by pleurisy with effusion. Mild bilateral pleurisy with effusion developing simultaneously with acute non-specific pericarditis is most common. Post-pneumonic pleurisy may be serous or purulent. In most cases it is serous and marked by a small or moderate amount of effusion. Examination of these patients reveals residual phenomena of pneumonia together with signs of pleurisy. These phenomena usually disappear spontaneously soon after pneumonia resolves.

Lymphocytes predominate in the cell composition of the effusion at first. When resolution of the effusion is delayed, their number gradually grows. Purulent pleurisy mostly develops after streptococcal pneumonia, which, fortunately, is rare. Purulent pleurisy often occurs in children in association with a staphylococcal infection and in the aged in association with pneumonia caused by *Friedländer's bacillus*. In rare cases pleurisy with effusion develops in attendance to diplococcal pneumonia, but the high incidence of this pneumonia results in the physician's seeing this type of pleurisy more frequently than the post-streptococcal form. Pleurisy with effusion often develops in other bacterial pneumonias

and in *parasitic diseases* (hydatid disease, amoebiasis, paragonimiasis).

Pleurisy caused by *malignant tumours*, carcinoma metastases in particular, is encountered more often in recent times. This is probably explained by the older age of the main contingent of patients and the considerable advance made in the surgical treatment of primary tumours. The pleural fluid may be serous or serohaemorrhagic and its relative density usually ranges from 1015 to 1018, i.e. it may be a transudate or an exudate. Accumulation of fluid in the pleural cavity is explained by involvement of the pleural layers in the tumour, combined with obstruction of the flow of pleural fluid by metastasis of the tumour to the pulmonary or mediastinal lymph nodes. Compression of the thoracic duct by the tumour or its metastases results in the entry of chylous fluid into the pleural cavity.

In lymphogranulomatosis and haematosarcoma, the pleural fluid accumulates mainly because the tumour tissue infiltrates the pleura. Obstruction to the flow of fluid from the pleura in these diseases is merely of auxiliary significance. That pleurisy with effusion is caused by lymphogranulomatosis or haematosarcoma may be presumed when enlargement of the lymph nodes at the root of the lung or in the mediastinum and signs of affection of the lung itself are found. The final diagnosis is established from the results of biopsy of the lymph node or examination of aspirated sternal contents.

Pleurisy in primary bronchial carcinoma may be serous or serohaemorrhagic. Tumours growing in the pulmonary root are complicated by pleurisy very rarely. A tumour arising from the bronchiolar epithelium is complicated by pleurisy in about 8 per cent of cases; pleurisy always develops on the involved side. The primary tumour is often very small and is only detected on the tomograms. Sometimes it cannot be seen at all. Metastases of the tumour in the mediastinal lymph nodes and root of the lung are often quite large. A peripheral tumour spreads to the pleura in some cases. When it causes stenosis of a bronchus, pneumonia often develops in the atelectatic segment. The final diagnosis is based on the results of bronchoscopy or bronchography and if these prove insufficient, also on the results of biopsy of the mediastinal lymph node. The detection of cells of the malignant tumour in the sputum or pleural fluid is a less reliable sign.

Carcinoma metastases in the pleura cause the development of serous pleurisy only in simultaneous involvement of the ducts draining the lymph nodes of the mediastinum, parenchyma and root of the lung. Pleural fluid in metastatic pleurisy is always rich in proteins, its relative density is often above 1018. Bilateral pleurisy is encountered as a rule in metastasis of carcinoma from the

liver and pancreas. A tentative diagnosis of metastatic carcinomatous pleurisy may be made after the primary tumour is found. The final diagnosis is established only when tumour cells are identified in the pleural fluid or carcinomatous nodes are found in biopsy of the pleura.

Primary pleural mesothelioma may be localized or diffuse. Localized mesothelioma is a benign tumour. It is rarely complicated by pleurisy with effusion. On the radiograph it is seen as a homogeneous shadow with clearly demarcated boundaries; it is located on the periphery of the lung. Diffuse mesothelioma is a malignant tumour and is always complicated by haemorrhagic pleurisy characterized by rapid collection of fluid after thoracocentesis. Despite the large amount of fluid in the pleural cavities, there is usually no displacement of the mediastinal organs, which is attributed to the rigidity of the diffusely thickened pleura. The final diagnosis is made from the results of pleural biopsy and the detection of characteristic tumour cells in the exudate.

Diffuse diseases of the connective tissue are often complicated by the accumulation of fluid in the pleural cavities, but pleurisy with effusion develops only in systemic lupus erythematosus and rheumatoid arthritis. In other diffuse diseases of the connective tissue fluid appears in the pleural cavity as a consequence of concomitant heart failure and not as a result of primary pleural involvement.

Serous pleurisy in systemic lupus erythematosus is mostly bilateral. Unilateral pleurisy usually forms on the left side. In very rare cases pleurisy with effusion is the first syndrome of systemic lupus erithematosus. In most cases it develops at the same time as pericarditis with effusion or myocarditis. The heart is always enlarged but its size changes characteristically rapidly, which is explained by the presence of the effusion in the pericardial cavity and then its resorption. The diagnosis of lupoid pleurisy may only be made in a patient suffering from systemic lupus erythematosus, i.e. if a polysystemic affection is found and lupus erythematosus cells are identified.

Pleurisy with effusion in rheumatoid arthritis appears sometimes after the onset of the articular syndrome. It is usually encountered in middle-aged males. Pleurisy with effusion in the periodical disease is discussed in the chapter 'Chest Pain'.

Pleurisy with effusion may be a consequence of *pulmonary infarctions* which often develop in the aged in heart failure, after bone fractures or surgery and when the patient is confined to bed for a long time because of some serious disease. Very often no sources of embolism are found in these patients. Pleural pain in the chest

with dyspnoea appear first and then may be joined by haemoptysis and fever in one or two days. The degree of the last two is determined by the size of the pulmonary infarct. A pleural rub is heard over the site of the infarct, but it soon disappears. A small effusion disappears spontaneously. Even greater effusions usually do not form after thoracocentesis.

Eosinophilic pleurisy is a condition in which a serous effusion complicates the course of pneumonia. A large number of eosinophils appear in the serous effusion in one of the stages of its development.

Effusions with a high content of eosinophils form sometimes in association with eosinophilic infiltrates in the lungs and periarteritis nodosa.

Pleurisy with effusion (usually haemorrhagic) develop sometimes in very severe *rheumatic fever*. In our experience simultaneous involvement of the serous membranes, lungs, pericardium, joints, peritoneum and signs of active myocarditis were encountered.

Supplement XXI-1

Causes of Accumulation of Fluid in the Pleural Cavity

1. Infections.
   - Bacteria, viruses, mycoplasma organisms.
   - Subdiaphragmatic abscess.
2. Tumours.
   - Lymphogranulomatosis, lymphosarcoma.
   - Metastasis of malignant tumour to the pleura.
   - Meigs' syndrome.
   - Mesothelioma.
3. Diffuse diseases of the connective tissue.
   - Systemic lupus erythematosus.
   - Rheumatoid arthritis.
4. Thromboembolism of the pulmonary artery.
   - Parietal thrombosis of a large branch.
   - Embolism of small branches (pulmonary infarction).
5. Injury.
   - Pneumothorax.
   - Haemothorax.
   - Chylothorax.
6. Other diseases.
   - Pancreatitis.
   - Myxoedema.
   - Lymphatic oedema.
   - Periodic disease.
   - Peritoneal dialysis and haemodialysis.
   - Dissecting aneurysm of the aorta.
   - Heart failure.
   - Constrictive pericarditis.

Diseases and Syndromes which Must be Differentiated from Accumulation of Fluid in the Pleural Cavity

1. Pneumonia.
2. Pleural adhesion.
3. Pulmonary or mediastinal tumour.
4. Fibrothorax.
5. Hydatid cyst of the lung.
6. Upward displacement of the diaphragm.

Chapter XXII

Pneumonia

Acute Pneumonia

Inflammation of the pulmonary parenchyma and interstitial tissue is called pneumonia. As many other clinical entities, it may be a primary disease or only a syndrome of a general disease. In the latter case pneumonia may be the first or one of the later manifestations of the disease.

Modern methods of pneumonia treatment are highly effective only when the specificity of the causative agent is identified. The possibilities and limitations of the clinical methods of examination used in the diagnosis of pneumonia should be known by every physician because the treatment of its bacterial forms must be started immediately after the tentative diagnosis is made, before X-ray examination is conducted and the results of special laboratory blood, urinary and sputum tests are obtained. This explains the close attention that is paid to the peculiarities of the clinical manifestations of the different types of pneumonia and their comparison with the findings of X-ray examination and laboratory tests.

It is known that the X-ray signs of pneumonia appear much later than the clinical signs. Even in acute lobar pneumonia they are often detected only on the second day of the disease. Zarnoza et al. (1976) reported fatal cases of pneumonia in which even repeated radiographs demonstrated no signs of infiltration of the lungs. The findings of the clinical examination of the patient should not be overestimated either. Every physician becomes convinced time and again that there are pneumonias in which respiratory murmurs do not change in character and there is no dull percussion note. A pneumonic foci in the region of the pulmonary root is nevertheless best detected by X-ray. The final diagnosis should be based in about the same proportion both on the character of the lung shadow and the character of the clinical manifestations of the disease. The entirety of the clinical findings also determines the true diagnostic significance of the results of blood tests and sputum examination.

In line with the classification of pneumonias according to aetiological principle accepted in the Soviet literature particular attention is paid to the clinical and laboratory signs which allow a tentative and then the final aetiological diagnosis to be made.

Since this book is intended for the practicing physician, pneumonias are grouped either according to the similarity of their clinical

manifestations or the specific features of their origin. The first tentative diagnosis of pneumonia is made on the basis of the medical history (often occupational) and the findings of the physical examination of the patient. The object of further diagnostic work lies in checking the tentative diagnosis and identifying the aetiology of pneumonia.

Bacterial (Gram-positive) Pneumonia

In most cases, bacterial pneumonia develops in attendance to acute respiratory diseases. This may possibly provide an explanation for what may be called the seasonal character of pneumonias. Their incidence is noticeably higher in winter and early spring than in summer. The number of cases with pneumonia increases sharply during epidemics of influenza. Influenza virus causes desquamation of the tracheal and bronchial ciliary epithelium and inhibits phagocytosis. Other diseases which reduce the protective properties of the body, e.g. diseases characterized by immune deficiency (myeloma, leukaemia, hypogammaglobulinaemia, etc.) and diseases leading to disturbances in the normal function of the ciliary epithelium (chronic bronchitis, bronchiectases, etc.) also predispose to pneumonia.

Diseases of the upper respiratory tract (sinusitis, pharyngitis, tonsillitis) promote aspiration of microorganisms into the trachea and bronchi. It was demonstrated in monkey experiments that total body cooling facilitates the penetration of diplococci from the upper into the lower respiratory tract. The following conditions predispose to the development of pneumonia: impaired function of the epiglottis, which is often encountered in epileptic seizures and diseases of the nervous system; respiratory disorders occurring in the postoperative period, under the effect of alcohol, chest injuries, diabetic acidosis, bronchial asthma and delirium tremens. Individuals with these pathological conditions must be considered particularly predisposed to pneumonia. As in the preantibiotic period, most pneumonias are now induced by streptococci and staphylococci.

Pneumococcal pneumonia is caused by *Streptococcus pneumoniae* (diplococcus), which had been known as pneumococcus for many years. The *Streptococcus pneumoniae* contains 84 serovaras which are agglutinated by the corresponding types of sera. Serovaras I, II, and III induce the severest forms of pneumonia. Pneumonias caused by serovar III are often attended by bacteraemia. The annual incidence of pneumococcal pneumonias is 1 or 2 cases per 1000 of population. They occur mainly among children of preschool age and aged individuals. This is explained by the fact that immunity to

the diplococcus has still not developed in the former but is diminished in the latter.

The disease sets in abruptly with a shaking chill after which continuous fever is established and chest pain and cough with red or rusty-coloured sputum appear. Signs of a preceding virus infection are found in more than half of cases.

The chill is the main initial symptom of the disease. It is encountered in approximately 80 per cent of cases and usually occurs as a single episode. Recurrent chills are observed only in individuals given antipyretics. Fever which is continuous as a rule is encountered almost in every patient. Large fluctuations of temperature occur only in patients given antipyretics and corticosteroids. In the aged, wounded or emaciated, and in patients with uraemia, body temperature may be normal. Just as fever of other aetiology, pneumonia is attended by eruption of herpetic vesicles in one fourth to one third of cases. They are usually found on the visible mucous membranes on the 2nd to 4th day of the disease. The appearance of recurrent chills with elevation of temperature in the evenings and its fall in the mornings is evidence that pneumonia is complicated by suppuration or that it is not of pneumococcal origin. Fever ends critically or by lysis, usually on the 5th, 7th, 9th, 11th or 13th day of the disease.

The rusty sputum is uniformly permeated with small vesicles of air. Because of a rich polysaccharide content it is so sticky that it remains glued to the bottom of an overturned spittoon. An admixture of bright red blood appears in the sputum in severe cases. In about 25 per cent of cases the sputum is mucopurulent.

The pleura is involved in the inflammatory process in about 70 per cent of pneumonia cases. Pain appears on the first day of the disease. Involvement of the diaphragmatic pleura, often occurring in pneumonia of the inferior lobe, may be marked by severe referred pain in the arms, forearms or the abdomen. Pneumonia of the right inferior lobe with radiation of pain to the right abdomen must sometimes be differentiated from acute cholecystitis or appendicitis. (This is discussed in greater detail in the chapter 'Abdominal Pain'.)

Severe pneumonia is marked by mild icteric colour of the skin, scleras and mucous membranes. The blood bilirubin (conjugated and unconjugated) concentration reaches 20-30 mg/l. Jaundice is encountered only in patients with streptococcal bacteraemia. Its development is attributed to the destruction of the red blood cells in the hepatized pulmonary lobe and to the formation of local necroses in the liver. The degree of toxicosis, cyanosis and dyspnoea varies in different patients.

The percussion note is dulled only when the focus of infiltration lies no deeper than 4 cm from the lung surface. Bronchophony and vocal fremitus are sometimes intensified a few hours before the

dullness appears. Bronchial respiration is heard over the entire or only over part of the involved lobe. In early prescription of antibiotics, respiration is usually diminished. Moist, usually fine bubbling and less frequently medium bubbling rales are always heard over the involved lobe of the lung. Sometimes they are sonorous, but more often they are dull.

In 95 per cent of patients the acute period of the disease is marked by leucocytosis with a shift of the differential count to the left; it rarely exceeds $15 \cdot 10^3$ to $20 \cdot 10^3$ per 1 μl (15 000 to 20 000 per 1 μl). In approximately 5 per cent of patients, the blood leucocyte count is normal.

The particular 'stickiness' of the sputum is explained by a high content in it of Gram-positive diplococci rich in polysaccharides. The Gram stain demonstrates a large number of neutrophils besides the diplococci in the sputum. Diplococcus is grown in the sputum culture. The great number of neutrophils in the sputum and growth of the pure culture could be assessed as laboratory verification of the diagnosis of pneumococcal pneumonia if it were not for the widely spread pneumococcus carriage.

Streptococci, morphologically indistinguishable from diplococci (the causative agents of pneumonia) are discovered in the nasopharynx of 5 to 50 per cent of healthy persons. This is why diagnostic significance should be attached not to the simple discovery of diplococci, but to their being discovered in great numbers and attended by a vast number of leucocytes. Streptococci may disappear from the sputum if the patient had been given antibiotics (practically every physician prescribes them now when pneumonia is suspected). Their absence from the sputum under the circumstances does not rule out the diagnosis of pneumococcal pneumonia. Isolation of the causative agent from the patient's blood is quite reliable proof of the aetiological connection of pneumonia with the diplococcus. It is isolated in about 30 per cent of patients.

In uncomplicated cases, infiltration of the lungs disappears completely two to four days after the crisis. Pneumonia caused by serovar III is sometimes complicated by necrosis of the lung and subsequent formation of an abscess. Small pleural effusions form in rare cases. Pleural empyema is encountered in less than 2 per cent of patients with pneumococcal pneumonia. Meningeal phenomena are found in most cases of severe pneumococcal pneumonia, but meningitis is among its very rare complications. Bacterial endocarditis, usually with affection of the aortic valve, develops simultaneously with meningitis. During our long years of hospital work we encountered haemorrhagic pericarditis only in three cases of pneumococcal pneumonia.

The high sensitivity of pneumonia-inducing diplococcus to penicillins and cephalosporins allows these antibiotics to be used for

diagnostic purposes. Their prescription leads to a sharp decrease in toxicosis and fever within one or two days in two thirds of cases of pneumococcal pneumonia. In about one third of cases treatment with these agents is less effective and causes normalization of body temperature in four to seven days. This is usually observed in patients with involvement of more than one pulmonary lobe and in individuals suffering from alcoholism. Pneumonias developing during treatment with full doses of penicillins, cephalosporins and erythromycins are most probably not of pneumococcal origin. There have been ever-increasing reports in recent years about tetracycline resistant diplococcal strains; therefore, pneumonias developing during tetracycline therapy may be pneumococcal.

Pneumococcal pneumonia begins in most cases on the periphery of the lung and its foci almost always adjoin the visceral pleura. This makes its diagnosis by means of physical methods of examination much easier. The foci of pneumococcal pneumonia are demonstrated on radiographs as homogeneous densities localized on the periphery of the pulmonary field in the early stages of the disease. When the whole lobe is involved, its volume on the radiographs does not diminish but rather even increases. The character of the spread of pneumococcal pneumonia is an important differential diagnostic sign. Segmental spread is hardly ever encountered.

In summing up the abovestated it may be said that the tentative diagnosis of pneumococcal pneumonia is based on the typical clinical and X-ray picture and the identification of a great number of Gram-positive *Diplococci pneumoniae* in combination with a great number of neutrophils in the sputum of a patient who had not been given antibiotics. The final diagnosis may only be made if *Streptococcus* (*Diplococcus*) *pneumoniae* is isolated from the blood, pleural fluid or bronchi of a patient with a clinical picture of pneumonia or when fluorescent antibodies to *Streptococcus* (*Diplococcus*) *pneumoniae* of a definite serovar are detected in the patient's blood by immune electrophoresis.

Staphylococcal pneumonia may either be an independent disease consequent upon infection conveyed by droplets or dust contained in the air or a complication of some other disease, e.g. sepsis. In the latter case the causative agent of pneumonia enters the lung by the haematogenous route. In hospitals for adults, about 5 per cent of all pneumonias are staphylococcal. The prognosis is extremely serious in all of them. Despite the use of all the available antibiotics, staphylococcal pneumonia mortality rate is still very high, reaching 30 per cent. Staphylococcal pneumonia is a secondary disease as a rule. Developing in attendance to measles, whooping cough, chronic bronchitis or other chronic diseases it sharply aggravates the patient's condition.

The clinical picture of staphylococcal pneumonia is very diverse

and is determined to a great measure by the patient's age. It always begins abruptly in children and is complicated by respiratory insufficiency in the very first days. In adults it often joins influenza or other acute respiratory diseases, usually in the period of recovery from them. Its onset is abrupt and marked by recurrent chills, pain in the side, and cough with purulent sputum often with an admixture of blood. Severe dyspnoea and frequently cyanosis also develop from the first days. Metastatic pneumonia in sepsis always begins abruptly and always aggravates the patient's condition very sharply.

The onset of staphylococcal pneumonia may also be insidious. This happens particularly often in postoperative patients and in those suffering from leukaemia, collagenosis or other severe diseases treated with corticosteroids and antibiotics. Staphylococcal pneumonia begins in them with fever and cough with purulent sputum containing an admixture of blood. Recurrent chills and chest pain are rare in such patients.

The physical signs of this disease hardly differ from those of pneumococcal pneumonia. Foci of dullness are rarely of bronchial, but mostly of diminished breathing with moist rales are usually heard over both lungs. Signs of fluid in the pleural cavity are often detected. A great number of staphylococci are found in the sputum. These bacteria are present in the upper respiratory tract of more than 50 per cent of healthy individuals. The aetiological association with pneumonia may be spoken of only when they are identified in very large numbers in the sputum.

In most cases staphylococcal pneumonia is marked by leucocytosis reaching $15 \cdot 10^3$ to $25 \cdot 10^3$ per 1 μl. In particularly severe cases the leucocyte count may be normal or even reduced. Abscess, empyema and pneumothorax are complications of pneumonia. Bacteraemia is found in 20 to 50 per cent of cases.

Staphylococci spread in the lungs only along the airways, and the foci of pulmonary tissue infiltration are therefore located in strict accordance with the boundaries of the pulmonary segments.

According to the severity of the infection, focal or homogeneous involvement of the segments is noted. The inflammatory effusion often fills the airways, leading to mild reduction in the volume of the involved segment and to the disappearance of the air bronchogram. In more than half the cases, involvement is bilateral. Abscesses, sometimes multiple, are found in approximately 50 per cent of the patients. The wall of these abscesses is thick, while the inner surface is uneven. Multiple pneumocele are often encountered in staphylococcal pneumonia, but they occur in other pulmonary infections too.

Thus, staphylococcal pneumonia differs from pneumococcal pneumonia in the character of the initial manifestations: recurrent chills, tendency to bilateral focal affection, predominantly of the

lower pulmonary lobes with the formation of pneumocele and abscesses, and a tendency to early development of respiratory insufficiency. The respiratory sounds are usually clearly audible in pneumococcal pneumonia while bronchophonia is intensified. Respiratory sounds and bronchophonia in staphylococcal pneumonia are usually diminished, because inflammatory effusion accumulates in the bronchus and because the inflammatory foci are located deeper. In pneumococcal pneumonia pain in the side is felt at the onset of the disease, but effusion rarely accumulates in the pleural cavity, and then usually after the fifth or seventh day of the disease. In staphylococcal pneumonia, effusion is revealed in the pleural cavity early, sometimes on the first or second day of the disease. This effusion is always sterile in pneumococcal pneumonia, but always purulent in staphylococcal pneumonia. The final diagnosis of staphylococcal pneumonia is made after the causative agent is isolated from the blood or the pleural fluid. Immune methods for the diagnosis of staphylococcal pneumonias have been recently proposed but we lack any experience in their application.

Streptococcal pneumonia is caused by Group A streptococcus which enters the lungs in droplets or dust in the aspirated air. Streptococcal pneumonia is now a rare disease. It accounts for less than 1 per cent of the total number of pneumonias. In most cases it is a complication of measles, whooping cough, influenza and other acute respiratory infections or chronic diseases of the lungs. Pharyngitis and tonsillitis are very rarely complicated by streptococcal pneumonia. With bronchogenic spread of the infection small foci of pneumonia are first located within the limits of a single segment. Interstitial localization of the foci makes it very difficult to detect them by clinical methods. In all our cases of streptococcal pneumonia a large number of small foci were revealed in the lower lobe of both lungs on the very first radiograph, while the findings of percussion and auscultation were very sparse and of little informativeness. Autopsy showed necrosis of the bronchial walls and multiple microabscesses in the peribronchial tissue with rupture into the pleural cavities.

The disease begins abruptly with a series of chills attended by fever, pain in the side, severe toxicosis and cough with liquid sputum containing a great number of streptococci. Severe dyspnoea and cyanosis develop within the first 24 hours. Rapid spread of the inflammation to the pleura is particularly characteristic. Pleurisy with effusion was encountered in 50 to 86 per cent of cases of streptococcal pneumonia. Its signs are usually detected on the first or second day of the disease. The liquid serous or serohaemorrhagic effusion always contains many streptococci. In the later stages of the disease, the effusion turns fibrinous and is evacuated from the pleural cavity with great difficulty.

High leucocytosis ($2 \cdot 10^4$ per 1 μl) with a marked neutrophil shift to the left is a characteristic sign. The frequency of bacteraemia is determined by the severity of the case. Streptococcal pneumonia is characterized by early development of anaemia and thrombocytaemia with purpura usually developing towards the end of the disease. In 10 to 12 per cent of cases the disease is complicated by purulent pericarditis.

A tentative diagnosis of streptococcal pneumonia is made in a patient with focal inflammation of the lungs complicated by pleurisy with effusion in the very first days. The discovery of almost a pure streptococcal culture in the sputum may be accepted as confirmation of this diagnosis. The final diagnosis is established after the streptococcus is isolated from the blood or pleural fluid. The diagnosis may be confirmed retrospectively according to the dynamics in the changes of antistreptolysin O titres.

Anaerobic pneumonia. The bacterial flora of the upper respiratory tract in a healthy person is distinguished for its constancy. About 10^7 aerobic and 10^8 anaerobic bacteria are contained in 1 ml of the nasopharyngeal secretions of a healthy person (Finegold, 1977). Any acute or chronic disease is marked by colonization of the upper respiratory tract by Gram-negative flora. The nasopharyngeal secretions are aspirated into the lungs during sleep in approximately 50 per cent of healthy and 70 per cent of sick persons (Huxley et al., 1978). The severer the patient's condition, the more is the number of anaerobic or mixed aerobic and anaerobic flora aspirated. Aspiration is particularly intensive in patients with dysphagia. Governed by the law of gravity, most of the aspirated bacteria enter the posterior segments of the upper and the apical segments of the lower pulmonary lobes.

Anaerobic pneumonia begins with a chill and chest pain. Fever of an irregular type with recurrent chills followed by profuse sweating and cough with fetid sputum are characteristic signs. In some cases there is no tissue necrosis in anaerobic pneumonia and therefore no fetid expectorations. In such instances anaerobic pneumonia does not differ clinically from pneumonias caused by aerobic bacteria or by mixed aerobic and anaerobic flora (Finegold, 1977).

A more massive anaerobic or mixed infection causes graver pneumonia marked by remittent fever, shaking chills, and high leucocytosis. The foci of pneumonia in such cases undergo early necrosis with the formation of microabscesses. On merging they may form a large cavity which in typical cases ruptures into the bronchus with a copious discharge of foul-smelling sputum. The presence of a fluid level on the radiograph is a further sign of pulmonary abscess. The inflammatory infiltrate around the abscess tends to spread in the direction of the pleura. Rupture of microabscesses into the pleura results in empyema.

Bacterial (Gram-negative) Pneumonia

It was established that 2 to 11.5 per cent of healthy persons and 60 to 75 per cent of patients with a chronic disease are carriers of Gram-negative bacteria (Johanson et al., 1972). Endogenous aspiration is evidently the cause of most bacterial Gram-negative pneumonias. Poorly sterilized medicinal aerosol sprayers, tracheostomy tubes, and equipment for artificial ventilation of the lungs may also be the cause of the dissemination of these bacteria in the lungs.

Haemophilus influenzae pneumonia. The Gram-negative influenza bacillus is often discovered in the respiratory tract of healthy persons. Its non-capsulated forms are detected in the sputum of 50 to 60 per cent of patients with chronic bronchitis. Capsulate forms of higher virulence are encountered much less frequently. The influenza bacillus was at first thought to be the causative agent of influenza, which explains its name. Later it began to be considered attendant to influenza diseases and the causative agent of acute catarrhs and secondary infections. It has recently been established that *Haemophilus influenzae* can itself cause pneumonia. Its capsulate serotypes usually induce lobar and segmental pneumonias of the inferior lobes of one or both lungs, while their noncapsulate serotypes are responsible for lobular pneumonias of the same localization.

The disease usually begins during or at the end of an exacerbation of chronic bronchitis or obstructive pulmonary emphysema. A chill or shivering fits are followed by fever, pain in the chest, and dyspnoea. The patient's general condition sharply deteriorates, particularly in cases of lobar and segmental pneumonias. In lobular pneumonia toxicosis is less intense. Physical examination yields little information because most of these patients have a long history of a chronic pulmonary disease which had caused marked changes in the percussion note and respiratory sounds. The information gained from X-ray examination of the patient is more reliable. It may demonstrate formely absent infiltration in the lower lobes of the lung in the form of a few foci or a homogeneous shadow extending over several segments, the entire lobe or several lobes of one or both lungs.

Leucopenia is often found at the onset, which later changes to leucocytosis with a shift to the left in the neutrophil series. Severe forms of pneumonia caused by capsulate *Haemophilus influenzae* (serovar b in particular) are often complicated by bacteraemia, pleurisy with effusion, and even empyema. A fatal outcome is encountered in 6 to 33 per cent of cases (Wallace et al., 1978). The aetiological diagnosis of pneumonia caused by *Haemophilus influenzae* may be made only when the causative agent is isolated from the sputum, bronchi, pleural fluid or blood.

Klebsiella pneumonia may be acute or chronic. Acute pneumonia (typical, or Friedländer's) is caused by the first three strains of *Klebsiella* genus whose growth is inhibited by many antibiotics. The other strains of this genus are resistant to most antibiotics. They usually induce pneumonia in chronic patients given antibiotics for a long time. This nosocomial infection begins insidiously and is distinguished by a chronic course.

It mostly attacks elderly and aged males suffering from alcoholism or cachexia caused by some chronic emaciating disease. In contrast to pneumococcal pneumonia, klebsiella pneumonia hardly ever develops in attendance to some disease of the upper respiratory tract. It occurs as an independent malady.

Acute klebsiella pneumonia always sets in abruptly with a chill, pain in the side, and cough. Fever may be of the continuous type (as in pneumococcal pneumonia) or remittent; in the aged it may be moderate or absent. The viscid sputum is coughed up with difficulty and resembles black-current jelly in appearance and consistency. Sputum, the consistency of jelly and stained with red blood, is often expelled. Mild jaundice develops in about 20 per cent of cases.

X-ray demonstrates homogeneous density extending over most or the entire pulmonary lobe. The distribution of infiltration foci in klebsiella pneumonia (just as in pneumococcal pneumonia) does not follow the segmental division of the lungs. They are usually localized in the posterior parts of the upper or the upper part of the lower pulmonary lobes. Only one (mostly the upper) lobe of the right lung is usually involved.

The physical methods of examination usually prove insufficient for detecting the foci of pulmonary infiltration. This is explained by obstruction of the bronchi by the jelly-like mucus, diminishing the respiratory sounds in the involved parts of the lung.

In two thirds of cases the disease is marked by moderate leucocytosis. In one third of cases the blood leucocyte count is normal. A large number of Gram-negative diplobacilli surrounded by a light capsule are seen in the sputum smear.

Klebsiella pneumonia is an extremely severe disease. Even with the application of adequate therapeutic methods the mortality rate is 25 to 50 per cent. The diagnosis of this disease must be discussed in all cases with severe pneumonia developing abruptly in a patient over 50 years of age. The most common findings in this pneumonia are remittent fever, mucous or jelly-like blood-containing sputum, and recurrent chills due to early formation of abscesses. A patient with acute pneumonia who had survived the first two days already has abscesses. In some patients, who had survived the acute period, pneumonia does not resolve completely and acquires a chronic course. Pneumosclerosis with bronchiectases and with one or more cav-

ities in the involved lung develops. In distinction from the sputum in fibrocavitary tuberculosis, the sputum of patients with klebsiella pneumonia is always found to contain the causative diplobacilli.

Coli pneumonia. The incidence of pneumonias caused by *Escherichia coli* has noticeably grown in the last decade. These pneumonias are mostly encountered in patients with diabetes mellitus, pyelonephritis, renal insufficiency and malignant tumours. All these patients are treated for a long time with antimetabolites and large doses of antibiotics under the effect of which the growth of normal microbial flora in the upper respiratory tract is suppressed and favourable conditions are created for the reproduction of *Escherichia coli*.

The *Escherichia coli* organisms are disseminated in the lungs either as a result of aspiration from the upper respiratory tract or by the haematogenous route. The latter is encountered particularly often in seriously ill urological patients.

The clinical manifestations of pneumonia are very diverse. The disease may set in gradually, in which event it is hard to detect it in a patient in whom the disease is already following a severe course. Sometimes pneumonia begins abruptly with a chill and is marked by an irregular-type fever. A patient whose condition is only moderately severe develops a cough with sputum containing a large number of Gram-negative bacilli. Bacteraemia occurs in 15 to 20 per cent of patients. The blood leucocyte count rises to $15 \cdot 10^3$-$20 \cdot 10^3$ per 1 μl in about one third of patients and is normal in the other two thirds.

Radiographs demonstrate lobular pneumonia. Some of the foci may merge and involve the entire lobe. The lower lobes are affected much more frequently than the upper lobes. The disease follows a severe course and is often complicated by bacteraemia and empyema. The mortality rate reaches 60 per cent.

The possibility of coli pneumonia should be weighed in every patient who had developed fever, cough and signs of lobular pneumonia during treatment with antibiotics and aerosols. The simple detection of a large number of Gram-negative bacilli in the sputum is not sufficiently convincing proof of the aetiological connection with pneumonia. The final diagnosis is based on the follow-up of the disease, e.g. from the coincidence in time of the appearance of Gram-negative bacilli in the sputum with the development of foci of lobular pneumonia and from the changes in the character of the fever. The diagnosis of coli pneumonia is considered hardly possible in a patient who had not been given antibiotics recently. To verify the diagnosis in such cases, it is necessary to isolate the bacillus from blood or pleural fluid.

Pyocyaneus pneumonia. The causative agent of this pneumo-

nia, *Pseudomonas pyocyanea*, is usually found in the faeces and on the skin of the axillary and inguinal regions. It disseminates in the lungs when it is aspirated from the upper respiratory tract during aerosol therapy or in artificial lung ventilation. Pyocyaneus pneumonia is mostly encountered in patients with acute leukaemia or pulmonary carcinoma and in patients given corticosteroids and immunosuppressant agents.

The disease is marked by an acute onset, recurrent chills, high fever, severe dyspnoea, cyanosis and cough during which a great amount of yellow or green sputum is expectorated. Many pneumonia foci are revealed in both lungs clinically. X-ray demonstrates confluent lobular pneumonia with most of the foci localized in the lower lobes. Early formation of microabscesses in the pulmonary tissue and empyema are characteristic signs. The mortality rate reaches 50 per cent.

Proteus pneumonia is usually encountered in alcoholics and in persons with chronic pulmonary diseases. It develops when the causative agent is aspirated into the lungs from the upper respiratory tract. Foci of homogeneous infiltration of the pulmonary tissue are found, as in cases of klebsiella pneumonia, in the posterior segments of the upper lobes. The onset is abrupt and the disease resembles klebsiella pneumonia in its clinical course. Multiple abscesses form in the lungs in the very first days. The prognosis is very serious in most cases because of the low sensitivity of the causative agent to many antibiotics.

Enterobacterial pneumonia is encountered in alcoholics, in persons suffering from bronchogenic carcinoma, epilepsy and burns, and in patients with artificial lung ventilation. It is a consequence of endogenous aspiration of the bacilli into the lungs from the upper respiratory tract and it is fully justified to call it the pneumonia of bacillus carriers. The onset is insidious and the disease is marked by irregular-type fever and expectoration of yellow purulent sputum. The foci of pulmonary infiltration are found in the lower lobes. No complications usually develop and the disease terminates in recovery in most cases. The mortality rate does not exceed 14 per cent.

Serratia pneumonia is caused by a Gram-negative bacillus inhabiting water, soil and foodstuffs. It is easily transmitted by hand contact, particularly in outbreaks of an infection of the urogenital tract. A person is usually contaminated during treatment with aerosols or when unsterilized instruments, e.g. tracheostomy tubes, aerosol sprayers or bronchoscopes are used (Webb and Vall-Spinosa, 1975). The pneumonic foci may be found both in the upper and in the lower pulmonary lobes.

The disease takes a very severe course with recurrent chills, fever of an irregular type and copious expectoration of mucus. It is very

difficult to treat serratia pneumonia, because the causative agent is highly resistant to most antibiotics. The mortality rate reaches 80 per cent.

Acinetobacterial pneumonia develops most frequently in patients with tracheostoma and endotracheal catheters. Endogenous aspiration of the causative agent from its habitats on the skin and nasopharyngeal mucosa is also possible. This route of infection is often encountered in alcoholics and in seriously ill patients. The disease begins abruptly and is marked by respiratory insufficiency and is often complicated by collapse. Clinical and X-ray examinations reveal foci of pneumonia predominantly in the lower lobes of both lungs. In about 50 per cent of cases the disease is complicated by abscesses and empyema. The final diagnosis is established when the causative agent is isolated from the blood or pleural fluid.

Other Gram-negative pneumonias. The causative agents of salmonellosis, whooping cough, plague, anthrax and other bacterial infections may induce pneumonia by the droplet or haematogenous route. Pneumonia proves to be nearly one of the manifestations of the principal disease. Pneumonias of mixed origin are sometimes encountered; for instance, pneumococcal or virus pneumonia may develop in a patient suffering from pulmonary tuberculosis. The choice of the therapeutic measures in such cases depends on the accuracy of the aetiological diagnosis.

Legionellosis (leginnaires' disease) is caused by the Gram-negative bacillus *Legionella pneumophila* and is encountered sporadically in the form of small outbreaks of pneumonia (Cordes and Fraser, 1980). The pneumonic form of the disease begins abruptly with fever, headache, myalgia and recurrent chills which are followed by profuse sweating. Body temperature rises to 39-40°C and stays at this level for two to seven days. Cough is dry or with mucopurulent sputum and lasts throughout the disease. Abdominal pain and watery diarrhoea sometimes occur before the onset of fever. Leucocytosis with a shift to the left in the neutrophil series is found at the peak of the fever.

X-ray examination demonstrates focal infiltration in one or both lungs. In an unfavourable course of the disease, some of the foci of infiltration merge with involvement of a segment or one or more lobes of one or both lungs. The results of clinical examination are determined by the spread of pneumonia. In cases of more extensive involvement, the percussion note is dull and a few moist rales are heard. Pneumonia is often complicated by the formation of a small pleural effusion, usually on one side. Resolution of pneumonia begins on the third week of the disease. If no specific treatment is applied, the mortality rate reaches 20 per cent.

The diagnosis of legionellosis should be presumed in every case of pneumonia marked by high fever, dry cough, recurrent chills

and diarrhoea, and which is resistant to the commonly applied methods of treatment. The final diagnosis is established retrospectively when the antibody titre in paired sera grows fourfold.

Virus and Mycoplasmal Pneumonias

Pneumonias are often encountered in virus diseases. They are caused either by the viruses themselves or by a secondary bacterial infection developing in attendance to the virus infection. Virus pneumonia usually occurs in the first days of the disease, whereas bacterial (secondary) pneumonia develops in the period of recovery from the initial disease. Depending on the size of the aerosol particles, specific respiratory viruses either reach only the upper respiratory tract or enter the trachea, bronchi, bronchioli and alveoli. Depending on the state of the body's defense forces and the virulence and dose of the virus, which had entered the respiratory tract, syndromes of affection of the upper or lower respiratory tract develop in a person.

Haemorrhagic effusion in the alveoli and polymorphocellular infiltration of the interalveolar septa are found in severe virus infection. Proliferation of bronchial, bronchiolar and alveolar epithelium and round-cell infiltration of the bronchial wall and peribronchial tissue are detected in mild cases. The main changes are concentrated in the interstitial tissue of the lungs and around the bronchioli and the blood and lymphatic vessels.

The disease begins insidiously, usually with cough which is dry or is marked by expectoration of a small amount of mucous or mucopurulent sputum. Body temperature may be subfebrile at first, but then may rise to 39°C on the second or third day of the disease. At times there are shivering fits, but a shaking chill never occurs. Physical examination reveals only diminished vesicular respiration and a few moist rales. Foci of a dull percussion note and bronchial respiration are revealed, but not in every case. The leucocyte count is normal or moderately increased and rarely exceeds $10 \cdot 10^3$-$12 \cdot 10^3$ per 1 μl. Bacterial pneumonia is presumed if the leucocyte count exceeds 15 000 per μl.

The foci of pneumonia are localized in the lower lobe, as a rule. Involvement of only one lobe is encountered in about half the cases. In affection of the upper lobe, the foci of virus pneumonia are sometimes mistaken for tuberculous foci. This error can be easily avoided if it is taken into account that usually only one lobe is involved in virus pneumonia.

A series of X-ray examinations shows that a fine reticular net corresponding to the pattern of the interstitial tissue of the involved pulmonary lobe is demonstrated at the onset of virus pneumonia.

In later stages the inflammatory process spreads also to the air-filled pulmonary tissue, which leads to the appearance of microfocal (acinose) densities. The process of recovery begins with resolution of the microfocal shadows, the intensified interstitial pattern of the lungs persists for two to four weeks.

Mycoplasmal pneumonia. *Mycoplasma pneumoniae* is the only mycoplasmal species pathogenic for man. It is also the most common cause of pulmonary inflammation of non-bacterial origin. It accounts for about 11 to 17 per cent of pneumonias in adults. The disease is encountered throughout the year with maximum incidence in late autumn and at the beginning of winter. It is asymptomatic in children of preschool age and mild in most adults.

Two or three weeks after infection, the patient experiences headache (sometimes severe), weakness, recurrent shivering fits, and moderate fever. Pain in the throat, rhinitis, and pain in the ear are sometimes observed. Cough is dry or with mucopurulent expectorations. An admixture of blood is found in the sputum in about 10 per cent of cases. Retrosternal pain, which is markedly intensified in coughing, is considered a characteristic sign. No less than 50 per cent of patients have relative bradycardia. Severe myalgia, arthralgia, the dyspeptic syndrome (nausea, sometimes vomiting), and diarrhoea appear in the initial period of the disease. Enlargement of the cervical lymph nodes and conjunctivitis are encountered in rare cases.

Fever lasts three to seven days. Cough, rales and foci of pneumonia in the lungs disappear in about three weeks. The second wave of fever sometimes appears seven to ten days after the first wave. It is induced by recurrent pneumonic foci. Approximately a fourth of the patients have a concomitant lesion of the pleura with accumulation of a small amount of serous or serohaemorrhagic effusion in it. In some cases, mycoplasmal infection coexists in the patient's body with other respiratory viruses, in others it develops in attendance to bacterial pneumonia or to other pulmonary diseases.

Auscultation reveals a few fine or medium bubbling rales. There are usually no foci of dullness of the percussion note, but X-ray surprisingly demonstrates focal shadows which are usually localized in the lower lobes of one or both lungs. Sometimes they are homogeneous, at other times they are of uneven density. Pneumonia resolves completely in four to six weeks. Blood changes are of no diagnostic importance. The acute period of the disease is mostly marked by moderate leucocytosis and less frequently by leucopenia.

Extrapulmonary manifestations of mycoplasmal infection occur very often and the tentative diagnosis may be made much easier if they are taken into account. Mycoplasmal infection is frequently complicated by autoimmune haemolytic anaemia with a positive

Coombs' test. Haemolysis begins two or three weeks from the onset of the disease. Anaemia and reticulocytosis are mild in most cases. Skin eruptions (polymorphic erythema, erythema nodosa, urticaria, etc.) appear in the first or second week of the disease in 25 per cent of patients. They disappear in one or two weeks. About one fourth of patients may develop pericarditis or myocarditis which is subclinical in most cases. Meningitis, meningoencephalitis, and myelitis appear sometimes in the second week of the disease.

The tentative diagnosis of mycoplasmal pneumonia is based on the combination of its characteristic signs (gradual beginning, paroxysmal cough) with retrosternal pain, relative bradycardia, absence of dyspnoea, and a discrepancy between the findings of the physical examination and the results of X-ray examination. In all cases of this kind, there is a confirmation of the saying 'very little heard, but very much to see'. The absence of sputum or the absence of bacteria in the expectorations and the above-described characteristic extrapulmonary manifestations of the disease are of certain assistance in making the diagnosis. The final diagnosis is established if the causative agent is isolated from the patient's sputum, pleural fluid or from the content of the vesicles erupted on the skin. Immune electrophoresis and complement fixation reaction have been applied lately in the diagnosis of mycoplasmal infection. A fourfold increase in the titre of specific antibodies during the disease is regarded as convincing verification of the clinical diagnosis.

Adenovirus pneumonia. Acute respiratory diseases caused by adenoviruses spread mainly in collectives, e.g. among children at pioneer camps or young recruits in the first months of their military service. Adenovirus infection is manifested by the syndromes of pharyngitis, pharyngoconjunctivitis, bronchiolitis, and pneumonia. The pathological changes in the lungs have still not been sufficiently studied. It can be concluded from the results of X-ray examination that adenovirus pneumonia is marked by changes similar to those found in mycoplasmal pneumonia. Involvement of the interstitial tissue of the lower pulmonary lobes predominates.

The disease begins insidiously with headache, recurrent fits of shivering, and general weakness. Body temperature in most cases does not exceed 38°C and stays on this level for two or five days. In rare cases it rises to 39.0-39.5°C. Signs of a more or less marked rhinitis are found in the first days of the disease in about 50 per cent of cases. Hyperaemia of the anterior pillars, soft palate and posterior pharyngeal wall are more common findings. Paroxysmal dry cough or cough with small amounts of mucopurulent sputum and retrosternal pain are encountered in almost every case of the disease. Pharyngitis and indisposition last one or two weeks. A few moist rales are sometimes heard on auscultation. X-ray examination (which is currently made in all patients with acute respir-

atory infections) demonstrates lobular pneumonia in about 10 per cent of cases.

Not only pharyngitis but follicular conjunctivitis (usually unilateral) is revealed simultaneously with adenovirus pneumonia in some patients. Adenovirus pneumonia is second among virus pneumonias in frequency. It is mild in most cases. The febrile period rarely exceeds seven days. The blood leucocyte count is normal. Leucocytosis occurs only when pneumonia is complicated by a bacterial infection.

The possibility of adenovirus pneumonia must be discussed in all cases of atypical pneumonia diagnosed in a patient with signs of pharyngitis or conjunctivitis. The final diagnosis is established when growth of the virus is produced in a culture. Among 31 serological adenovirus vars only three (types III, IV and VII) are capable of producing an acute respiratory disease in a human.

Influenzal pneumonia. Influenza viruses are endemic in all parts of the world. Pneumonia is rarely encountered in cases of sporadic influenza, but its incidence noticeably increases during epidemics. The aspirated particles of influenza virus penetrate the epithelial cells of the upper respiratory tract and cause their necrosis. The affected cells desquamate into the lumen of the trachea and bronchi and obstruct the bronchioli. Bacterial infection of the de-epithelized surface produces inflammation of the tracheal, bronchial and bronchiolar walls and spreads peribronchially to the alveoli. Pneumonia is of mixed origin in most cases. Much less frequently pneumonia develops under the effect of influenza virus alone.

Cases of severe influenza begin abruptly with a sensation of drastic weakness, dizziness, severe headache, and recurrent chills which, however, are never of a shaking character. Fever may be as high as 39-41 °C even in cases of influenza uncomplicated by bacterial infection. All these symptoms are followed by pains in the eyes and in all muscle groups of the body, a feeling of powerlessness and, sometimes, by vomiting. Signs of upper respiratory catarrh are mild in such cases. They even may not develop for a long period of time. General weakness predominates in the clinical picture of the early period of the disease. Catarrh of the upper respiratory tract (pain in the throat and retrosternal pain, cough, hyperaemia of the conjunctivas), though present in most patients, is mild and in no way can be the cause of prostration.

In cases of uncomplicated influenza fever and prostration last two to five days, after which body temperature falls and signs of secondary bacterial infection come to the forefront. Dry cough changes to productive cough, and rales appear in the lungs. Patients usually recover in seven to ten days. Recovery is delayed only in patients suffering from heart failure or chronic pulmonary diseases. Necrotic laryngotracheobronchitis may lead to respiratory insuf-

ficiency and cyanosis, for the management of which tracheotom is sometimes resorted to.

Primary virus pneumonia usually develops in the first days (the main disease. Its principal signs are prostration, severe dy pnoea with diffuse cyanosis, copious expectoration of bloody sputun and a large number of consonating and moist rales heard in bot lungs. Physical methods of examination usually fail to reveal sig of inflammatory infiltration of the pulmonary tissue in this peric of the disease, but radiographs demonstrate focal rounded or irre ularly shaped densities in both lungs. They roughly correspor to the severity of the disease in number and size. In the followir days, the continuously high fever is joined by progressive respir tory insufficiency and collapse. Death usually occurs in the fir week of the disease. Mild cases of primary influenzal pneumonia a characterized by less extensive changes in the lungs and modera cyanosis. Arterial pressure is within normal values. In young ar middle-aged patients with no signs of heart failure or chronic pu monary disease, pneumonia may undergo involution.

Secondary bacterial pneumonia develops in concomitance wi influenza in the later stages of the disease in most cases, usual after the fever has subsided. The improvement which has just start is replaced by an exacerbation of the disease. Fever and cough wi purulent sputum reappear. Physical and X-ray examinations di close signs of segmental or lobar infiltration of the lungs. In t past, bacterial pneumonia was often caused by streptococci; at pre ent it is usually produced in influenza by *Haemophilus influenz* or by staphylococci. Additional infection with the former micro aggravates the patient's condition only slightly, whereas infecti with staphylococci terminates in the formation of pulmonary a scesses or empyema.

The leucocyte count in uncomplicated influenza is usually n mal; leucocytosis is encountered from the first day of primary vir pneumonia. The number of lymphocytes in the blood decreases the first four days of the disease, later lymphopenia disappea The concomitant development of secondary bacterial infection attended by a rise in leucocytosis, the level of which is determin by the severity and character of the complication.

During epidemics, a tentative diagnosis of influenza and influen pneumonia is easily made on the basis of the clinical criteria scribed above and the epidemiological situation. It is far more d ficult to establish the exact diagnosis of influenza in a period betwe epidemics. It should be borne in mind that cases of sporadic influ za are usually uncomplicated by primary (virus) pneumonia. T final diagnosis is established by immunofluorescence of influen antigens in stained imprints or washings from the nasal or na pharyngeal mucosa. The method yeilds positive results in appro

mately 50 per cent of influenza cases. The exact diagnosis may be made by obtaining pure growth of the causative agent in cultures of the washings from the nasal and throat mucosa.

Influenzal pneumonia is distinguished from adenovirus pneumonia by sharply marked signs of toxicosis, collapse, and the absence or the presence of very mild pharyngitis or pharyngoconjunctivitis syndrome.

Other virus pneumonias. Lobular or confluent pneumonias in adults are caused in rare cases by other viruses responsible for acute respiratory infection, namely, respiratory syncytial virus, cytomegalovirus, rhinovirus and enterovirus. Besides, pneumonia is sometimes induced by chickenpox, measles, lymphocytic choriomeningitis, and herpes zoster viruses. The inflammatory process in these pneumonias is mainly localized in the interstitial tissue and it is therefore much more difficult to distinguish them by physical methods of examination than by X-ray. They are also often complicated by a bacterial infection.

Chlamydian and Rickettsial Pneumonias

Ornithosis pneumonia is caused by *Chlamydia psittaci* and encountered among huntsmen and employees of poultry farms who contact domestic or wild fowl. The source of infection in towns are street pigeons among which 30 to 80 per cent are contagious. In rare cases, warblers and decorative birds become the sources of infection. The causative agent enters the body through the respiratory tract in most cases. According to Kazantsev (1981), approximately 20 per cent of all pneumonias in Leningrad are induced by the causative agent of ornithosis.

In most cases, the disease begins with a chill and elevation of body temperature to 38-39°C. Dry cough with a burning retrosternal sensation and marked toxicosis with headache, jadedness, insomnia, arthralgia, periarthritis and muscle pain, which is particularly sharp in the neck and small of the back, appear in the first days. Fever (continuous or remittent) lasts 5 to 12 days. In cases of greater severity, a rosy macular or papular eruption forms on the extensor surface of the limbs on the third or fourth day of the disease.

Fine bubbling rales are heard against the background of harsh breathing over the lower pulmonary lobes from the first days of the disease. They gradually increase in number. The clinical signs of pulmonary infiltration are not determined, but X-ray examination demonstrates a great number of microfocal, at times merging, shadows mainly localized in the lower lobes of the lungs. In 20 per cent of cases, a second wave of fever due to the development of a concomitant bacterial infection occurs while the pneumonia is still unre-

solved. The clinical signs of this secondary pneumonia are manifest more clearly. A second wave of fever may also be caused by a recurrence of the principal disease, in which toxicosis is less manifest, and which develops two or four weeks after the first wave of fever subsides (Ilyinsky, 1974).

It is simpler to make the diagnosis of ornithosis pneumonia when extrapulmonary signs of the main disease appear in the febrile period, namely, encephalitis, meningitis, epileptic seizures, myocarditis, haemolytic anaemia, hepatitis, pancreatitis, proteinuria and splenomegaly. These signs are not constant and found mostly in severe cases of the disease. The tentative diagnosis of ornithosis pneumonia is based on the combination of the clinical syndrome described above with information on the patient's occupation and his contact with birds. To establish the final diagnosis it is necessary in addition to these data either to isolate *C. psittaci* from the patient's sputum or blood or to detect at least a fourfold increase in the titre of the complement-fixation reaction with the ornithosis antigen in paired sera.

Pneumonia in Q fever begins abruptly. It is mainly encountered among workers of slaughtering houses and dairy farms. Elevation of body temperature to 39-40°C is attended by a shaking chill which is replaced by profuse sweating. Severe headache, rigidity of the occipital muscles, drastic weakness, insomnia, pain in the throat and dry cough appear at the onset of the disease. The fever lasts one week in most cases. Rare cases are marked by long-term fever and involvement of many internal organs.

Examination of the lungs in the febrile period reveals only a few fine bubbling rales, whereas X-ray usually shows many focal shadows localized predominantly in the lower pulmonary lobes. The signs of lobular pneumonia ordinarily disappear without treatment (Baum, 1974). In many cases, Q fever takes a chronic course with the development of vasculitis and involvement of the liver (hepatitis), heart (myocarditis, pericarditis, endocarditis most frequently with aortic valve affection), eyes (uveitis, neuritis of the optic nerve) and meninges.

Q fever may be suspected when pneumonia occurring in combination with extrapulmonary manifestations of the disease develop in persons of certain trades. The final diagnosis is established when the clinical picture of pneumonia is combined with positive agglutination test or complement-fixation reaction in paired sera. The latter should be made no earlier than the third week of the disease.

The methods used in the treatment of bacterial pneumonias noticeably differ from those applied in virus pneumonias. This is why the issue of their diagnosis acquires practical importance apart from purely academic interest. It is much easier for the physician to make the differential diagnosis between these large clinical syndromes a

the patient's bedside if he takes into account that bacterial pneumonia begins with involvement of the air passages, whereas virus pneumonia is characterized by early involvement of the interstitial pulmonary tissue. This difference in the pathogenic processes underlies most methods used in the clinic for the differential diagnosis of these syndromes. It is precisely this phenomenon that explains why infiltration of the lungs in bacterial pneumonia can almost always be disclosed by percussion and why its timely detection in virus pneumonia requires X-ray examination.

In identifying the cause of pneumonia, it is necessary before all else to pay special attention to the patient's general condition. Bacterial pneumonia is mostly encountered among the middle-aged and elderly. Their condition deteriorates sharply from the very first days of the ailment and the physician finds them to be gravely ill on his very first visit. They are often even incapable of moving around the room and are obliged to keep to bed for lack of strength.

Virus pneumonia attacks mostly the young. One does not gain the impression at the onset of the disease that they are seriously ill. The sole exception is influenza pneumonia, but its diagnosis is made easier by the fact that it is encountered almost exclusively during epidemics of this disease. In most cases, virus pneumonia is an acute but not a severe disease, whereas bacterial pneumonia is an acute and grave, or even very grave malady.

Bacterial pneumonia sharply differs from virus pneumonia in the initial manifestations. The former always begins abruptly. The patient himself or his domestics can indicate without error the day and hour the disease had begun. Persons in sound health before the onset of bacterial pneumonia suddenly develop a shaking chill or a series of marked chills followed by elevation of body temperature to 39°C, sometimes even to 40°C and more. Pain in the side appears with the outbreak of fever, but there is no muscle pain. Virus pneumonia usually sets in insidiously. The patient's condition gradually deteriorates in one or two days and he experiences mild fits of shivering. Fever does not exceed 39°C. Myalgia appears in the period of indisposition and persists in the febrile period of the disease.

Cough is a sign which in most instances helps greatly in making the differential diagnosis between bacterial and virus pneumonias. Severe paroxysmal cough without expectoration combined with a burning retrosternal pain is regarded among the typical signs of virus pneumonia. Dry cough is encountered only in the first one or two days of bacterial pneumonia. Later, sticky sputum with an admixture of blood is expectorated. The appearance of chest pain in coughing is attributed to involvement of pleura adjoining the pneumonic foci in the inflammatory process. Leucocytosis is always detected in the sputum of a patient with bacterial pneumonia and also

the causative agent in patients not treated with antibiotics. In most instances the sputum of a patient with virus pneumonia does not contain purulent cells. A great number of saprophytes inhabiting the upper respiratory tract may be found in it.

Dyspnoea and tachycardia appear on the first day of bacterial pneumonia. Cyanosis joins them in severe cases. The respiratory rate in virus pneumonia usually does not change. The heartbeat is normal or somewhat decelerated. Influenza pneumonia whose clinical picture is described above is an exception. Bacterial pneumonia in the aged and in alcoholics is often complicated by delirium or other behavioural disorders. Delirium or other types of excitation are very rare in virus pneumonias.

In bacterial pneumonia, pulmonary infiltration usually spreads unilaterally involving a segment or lobe. Virus pneumonias are bilateral in most cases. Foci of this pneumonia, in influenza, for instance, affect both lungs diffusely. The scarcity of auscultative signs of virus pneumonia is explained by the absence of the connection of its foci with the airways of the lungs.

Clearly expressed leucocytosis is encountered in almost every case of bacterial pneumonia. In virus pneumonias, with the exception of influenza pneumonia, there is no leucocytosis in the first week; bacterial pneumonia often develops in conjunction with it in the second week of the disease. The blood leucocyte count increases noticeably in such cases and may reach $15 \cdot 10^3$-$20 \cdot 10^3$ per 1 μl.

The differential diagnostic importance of trial antibiotic therapy should now be appraised with proper caution. The normalization of body temperature 48 hours after the prescription of antibiotics and the abatement of toxicosis may be accepted as indirect evidence of bacterial pneumonia. The absence of such a rapid effect does not rule out the disease, because this may be the result of the resistance of the bacterial strain to the antibiotic or the insufficient dose of the agent, allergic reaction to the antibiotic, and the association of fever with another disease (e.g. malignant tumour, collagenosis) or with early pulmonary suppuration.

An intensive homogeneous density of an entire lobe is often appraised as a characteristic sign of bacterial pneumonia. Density in mycoplasmal and virus pneumonias is distinguished by nonhomogeneity and lesser intensity. A small pleural effusion and pneumothorax sometimes develop in bacterial pneumonias but are not typical of mycoplasmal and virus pneumonias. Pneumocele is not encountered in mycoplasmal or virus pneumonias but is an important diagnostic sign of staphylococcal pneumonia. The early formation of a cavity in the lung occurs in bacterial pneumonias and in pulmonary tuberculosis but is not encountered in virus pneumonias. Bacterial and virus pneumonias can be distinguished in most cases from pneumonia in ornithosis and Q fever because these

two diseases are marked by signs of simultaneous affection of the lungs and other organs.

The role of all the above-listed signs in the differential diagnosis of pneumonia should not, however, be overestimated. Even repeated clinical and X-ray examinations combined with repeated examinations of the sputum often prove insufficiently informative for identifying its cause. The aetiological diagnosis of pneumonia may often be made only by means of invasive methods of examination including isolation of the causative agent from the washings of a segmental and, still better, a subsegmental bronchus, needle biopsy of the pulmonary tissue or biopsy of the regional lymph node during bronchoscopy and, in occasional cases, also thoracotomy.

Allergic Pneumonias

Pneumonias induced by aspiration of organic dust. Three stages are distinguished in the development of allergic pneumonia according to the comparison of clinical and anatomical data. A picture of acute vasculitis with fibrinous thrombi in the vessels is found in the interalveolar and interlobar septa of the affected lung in the second week of the disease. The connective tissue of the lung is infiltrated with neutrophils, eosinophils, lymphocytes and plasma cells. Acute inflammation of the bronchioles ls often attended by destruction of their walls. A picture of interstitial pneumonia and granuloma with Langhans' giant cells is discovered in the involved lung one or two months after the onset of the disease. The granuloma disappears a few months later. Lobular or diffuse reticular pneumosclerosis resembling honeycombs in structure is seen in the lungs.

The onset of the disease in most cases is insidious with general weakness, anorexia to which pain in the trunk muscles develops in attendance. Dyspnoea and cough appear only on effort at the onset of the disease but become permanent later. Body temperature is usually elevated to 38-39°C with chills. Auscultation reveals only a few fine bubbling rales in both lungs. In some cases body temperature is normal.

Much less frequently (in about a third of cases) the disease begins abruptly with a chill and rise in body temperature to 38-39°C. Dyspnoea, cough, sometimes with a small amount of blood-stained sputum, marked jadedness increase the resemblance of the disease with virus infections. Moist rales are heard in the lungs. The patient's condition improves rapidly a few hours after hospitalization, but the moist rales may be heard in the lungs for several days. The described acute attack of the disease may recur. It is induced by repeated

contact of the patient with the aetiological factor, e.g. with substances contained in mouldy hay, decaying straw, mushrooms and sawdust.

Leucocytosis sometimes reaching $25 \cdot 10^3$ per 1 μl is found in the blood in the acute period of the disease Eosinophilia is not a constant or frequent sign of this group of diseases, but in some cases the blood eosinophil content increases to 10 per cent. The content of immunoglobulins in the blood rises noticeably. The concentration of immunoglobulin G increases particularly often.

The radiograph shows no changes at the onset of the disease. Small punctate (up to 1 mm in diameter) shadows scattered diffusely in both lungs are found in recurrent exacerbation of the disease and in chronic cases. These shadows may be discrete (as in acute left-ventricular failure, influenza) or confluent. Diffuse nodular shadows with poorly demarcated outlines are seen in both lungs in graver cases. Chronic cases of the disease are marked by a reticular structure of both lungs characteristic of interstitial fibrosis and emphysema of the lung.

The diagnosis of the disease is based on the medical history for which it is necessary to question the patient about the circumstances of the development of the first and subsequent attacks of the disease. Special attention is focused on the patient's occupation, the connection of the clinical signs of the disease and the degree of their manifestation on and off the job. Considerable diagnostic importance is attached to the trial contact of the patient with the suspected antigen. Immunoelectrophoresis of the patient's serum with the suspected antigens is a specific method for the diagnosis of allergic pneumonias. Skin tests are insufficiently specific and often yeild erroneously positive results.

'Farmer's lung' is the most closely studied type in this group of pneumonias (after berylliosis). A mass-scale outbreak of this disease recently occurred among Czechoslovakian students who worked at a farm drying and handling grain cultures. It is known that this disease sometimes occurs among farm workers handling grain, working at the threshers, stacking the harvest, and those engaged in the primary processing of flax and hemp. In most cases the disease is caused by inhaled thermophilic actinomycetes *Thermopolyspora polyspora* and *Micromonospora vulgaris* which multiply in moist hay.

Mushrooms are cultured under high temperature and humidity which likewise promote the growth of thermophilic actinomycetes Workers engaged in this production sometimes develop fever, cough dyspnoea, myalgia, vomiting and other signs of allergic pneumonia described above. Leucocytosis at times reaches $25 \cdot 10^3$ per 1 μl Moderate eosinophilia is found in some cases. Pneumonia in patient with the 'lung of a mushroom picker' is attended by enlargement o

the regional lymph nodes at the pulmonary root and resembles involvement of the lungs in sarcoidosis.

Begascosis is the name given to a disease developing in workers engaged in processing sugar cane. Its clinical picture corresponds to that of the described allergic pneumonia. The patient's blood contains precipitins to extracts from material remaining in the plant after sugar has been removed from them, and to extracts of the thermophilic actinomycete *Micromonospora vulgaris*. The actinomycete is also revealed in the blood of patients who had inhaled dust forming when sugar cane is being processed. Radiographs reveal diffuse lymphatic shadows in no way different from the picture typical of miliary tuberculosis. The clinical picture of the disease does not differ from that of 'farmer's lung'.

'Bird fancier's lung' is marked by the same symptoms and signs as 'farmer's lung'. They only differ in the cause of the disease. The clinical spectrum from an acute attack of paroxysmal dyspnoea to diffuse microfocal pneumonia, which occurs in this disease, is produced under the effect of contact with the protein of shedded pigeon's feathers or pigeon droppings. The serum of pigeon fanciers suffering from pneumonia contains precipitins to the mentioned antigens. Radiographs may demonstrate micropunctate interstitial pneumonia. Acinose foci appear in occasional cases which is evidence that the air-filled pulmonary tissue is also involved in the process.

Powder prepared from the pituitary gland of neat cattle or hogs has been long used for the control of diabetes insipidus. Its long-term application to the nasal mucosa at times results in the sensitization of the body. Precipitating antibodies to the proteins contained in this inhalant powder appear in the blood of patients with diabetes incipidus. Miliary shadows form in the lungs in prolonged use of the powder. Lung biopsy allowed the morphological substrate of this pneumonia to be established. A fibrinoid effusion was found in the alveoli with the formation of hyaline membranes and lymphocytic and plasma cell infiltration of the pulmonary connective tissue.

Allergic pneumonia sometimes develops in sawers, workers processing cork, making malt and employed in many other productions. The same clinical picture is common in all such cases. The underlying factor is an inflammatory process in the interstitial pulmonary tissue which may be designated 'allergic interstitial pneumonia'. In practice it must be differentiated from other diseases of the lungs marked by eosinophilia and from many non-specific pulmonary diseases producing a similar X-ray picture. Before all else they must be distinguished from interstitial pneumonias developing in virus infections with which they are always similar both in clinical manifestations and in the results of X-ray examination, and from other pneumonias marked by eosinophilia.

Virus interstitial pneumonias terminate in most cases in recovery even if they are not treated. The tendency to a spontaneous cure distinguishes them sharply from allergic pneumonias which always tend to take a progressive course unless treated. Allergic pneumonias result from the interaction of the patient with the antigen. Removal of the sick person from production, i.e. cessation of his contact with the antigen in the early stages of the disease, always leads to clinical recovery, whereas his return to production inevitably results in a recurrence of the disease. Virus infection leaves a more or less long-term immunity and the recurrence does not occur when the person resumes his job.

Virus pneumonia is distinguished most reliably from allergic pneumonia by isolating the pure culture of the causative agent or by repeated immunity tests showing a growth in the antibody titre. The diagnosis of allergic pneumonia is verified by identifying in the patient's blood specific antibodies to antigens contained in organic dust. Allergic pneumonia is often combined with paroxysmal dyspnoea and eosinophilia. It must therefore always be distinguished from pulmonary aspergillosis, which is also marked by attacks of paroxysmal dyspnoea, permanent eosinophilia and often by microfocal pneumonia. Permanent eosinophilia, a positive test for the antigens from *Aspergillus fumigatus* and information on living and working conditions, which have a bearing on the given disease, make differentiation of these diseases possible.

Loeffler's syndrome (infiltrates in the lung with eosinophilia) is the mildest and most frequent in the group of diseases marked by eosinophilia and transient ('migrating') infiltrates in the lungs. Biopsy shows that these infiltrates are foci of pneumonia whose inflammatory effusion contains many eosinophils and sometimes also Langhans' type giant cells.

The clinical manifestations of the disease are diverse. Some patients have no complaints, whereas in others a picture of severe pneumonia with marked dyspnoea and high fever develop. Cough may be dry, but in most cases it is productive. The sputum is yellowish and contains many eosinophils. The percussion note above superficial foci is dulled, respiration is usually diminished and there are few fine-bubbling rales. Some patients are very weak and suffer from headache and sweating at night, which, in combination with a subfebrile temperature, provides grounds for presuming tuberculosis in a patient. This presumption is reinforced after X-ray demonstrating a pulmonary infiltrate. A blood test shows leucocytosis, sometimes of up to $20 \cdot 10^3$ per 1 μl. The eosinophil count does not exceed 10 per cent in mild cases, but reaches 25 per cent in severer cases.

X-ray demonstrates solitary or multiple foci of density in one or in both lungs of a homogeneous or non-homogeneous character.

Their outlines are not clear. These densities are usually localized in the lateral parts of the lung, and extend to parts of several segments. The intensity and size of the densities may change within very short terms which is why they are described as 'quickly passing'. The disappearance of infiltrate from one part and its formation in another part of the lung are sometimes encountered.

Foci of allergic pneumonia develop most frequently in association with the migration of ascarides, ankylostomas, the *Opisthorchis* liver fluke and other helminths. A less frequent cause of their development are antigens of plant origin, particularly the pollen of *Laurus nobilis*, *Convallaria majalis* and other plants. In recent times there have been frequent reports on the development of Loeffler's syndrome due to the effect of drugs, namely, para-aminosalicylic acid, penicillin, sulphonamides, nitrofurantoin derivatives (furadonin, etc.) and acetylsalicylic acid.

In mild cases of Loeffler's syndrome fever lasts no longer than one or two weeks. The pulmonary infiltrate disappears by about the same time. In severe cases high fever may persist for one or more months. Infiltrates in the lungs may occur simultaneously with infiltrates in other organs. Foci of inflammation develop with particular constancy in the pleura (leading to the formation of eosinophilic pleurisy), in the mucous membrane of the nasal sinuses, in the liver and in the spleen. Only once we observed the formation of eosinophilic infiltrate in the urinary organs, which was attended by long-term discharge of a great number of eosinophils into the urine.

Fever, hepatomegaly and accumulation of fluid in the pleural cavity sometimes persist for six to eight months, but in all cases the disease terminates in full recovery. Haemoptysis, not copious as a rule, sometimes occurs. The appearance of paroxysmal dyspnoea and many dry rales indicates that it is necessary to reconsider the diagnosis of Loeffler's syndrome and discuss the possibility of bronchial asthma induced by *Aspergillus fumigatus* antigen or by other antigens of plant or animal origin.

Pneumonias Caused by Certain Physical and Chemical Factors

Lipoid pneumonia. Exogenous and endogenous forms of this pneumonia are distinguished. The first form is caused by aspiration of animal fats and mineral and vegetable oils. The second occurs in fatty embolizations of the lungs.

Exogenous lipoid pneumonia is most commonly induced by aspiration of fluid paraffin widely prescribed as a purgative and as nasal drops. Mineral oils may also be aspirated by adults violating

safety rules when cleaning aircraft with vapourized oil. Liquefied fats of plant or animal origin often enter the respiratory tract of children when they are given milk with cod liver oil or with melted butter in it. It is also encountered quite often in adults suffering from diseases of the oesophagus (strictures, diverticula, achalasia, etc.) or dysphagias which are commonly associated with disturbed activity of the bulbar centres.

Mineral oils are chemically inert. Having gained entrance into the lungs, they are rapidly emulgated and engulfed by the macrophages. They are ultimately removed from the lungs by way of the lymphatics. In aspiration of a considerable amount of mineral oil, some of it is retained in the respiratory tract and becomes the cause of pulmonary fibrosis. Most vegetable oils are emulgated by pulmonary lipase and removed from the respiratory tract by coughing. Fats of animal origin are hydrolized by pulmonary lipase. The fatty acids which are liberated in the process induce severe inflammation the end result of which is sclerosis of the involved part of the lungs.

Most patients have no complaints and the affection of the lungs is often found by chance during X-ray for some other reason.

Aspiration of fats of animal origin leads to pneumonia mostly localized in the lower lobes. Suppuration of the lungs may develop if there is a concomitant secondary infection. X-ray examination demonstrates homogeneous densities usually extending to one or two segments of the lower lobes of both lungs. The shadow characteristically fits the boundaries of the affected segments. The edges of the sclerosed segments are clearly outlined. A granuloma closely resembles the shadow of peripheral pulmonary carcinoma and is often mistaken for it. In diffuse affection, interstitial pneumonia develops and terminates in diffuse-reticular pneumosclerosis and cor pulmonale.

The diagnosis is very difficult. Exogenous lipoid pneumonia may be presumed in sick individuals handling mineral oils or those who take paraffin oil as a purgative for a lengthy period of time. If the oil had been aspirated comparatively recently the patient may recall that the disease had begun with paroxysmal dyspnoea and cough which occurred after awkwardly swallowing food during a meal. Patients with disturbed swallowing and those with diseases of the oesophagus are particularly inclined to develop this type of pneumonia.

Hydrocarbon pneumonia. About 25 per cent of all household poisonings in children are due to aspiration of hydrocarbon compounds. The wide use of these compounds in industry, transport and everyday life sometimes leads to their inhalation or aspiration by adults. Substances which are more frequently aspirated or inhaled are petrol, kerosene, polishing liquids, irritating and asphyx-

iating substances (nitrogen oxides, gunpowder or explosive gases, gas-electric welding aerosol).

Accidental swallowing of hydrocarbons is attended by vomiting during which they are aspirated into the respiratory tract. The clinical picture of the disease is determined by the dose of the aspirated agent. Aspiration of a more or less considerable amount of any of these hydrocarbons causes bronchospasm which may be complicated by pulmonary oedema. Absorption of petrol from the lungs may lead to affection of the liver, kidneys, heart, and central nervous system. Shock or coma develops in particularly severe affection. If the patient survives the acute period, in six to eight hours he develops pneumonia with neutrophilic leucocytosis, dyspnoea, tachycardia and physical signs of pulmonary tissue infiltration.

The X-ray picture depends on the period of the disease. Pulmonary oedema, in most cases bilateral and symmetric, is found in the earliest period. Macrofocal densities with blurred outlines usually develop later. On merging they produce a picture of pseudobacterial pneumonia. The lower pulmonary lobes are mainly involved. Clinical recovery occurs much earlier than anatomical recovery. The diagnosis is based on the case history and, if there are no witnesses to the accident, it is testified to by the odour, for instance of petrol, from the patient. The acute disease may develop into chronic proliferative inflammation of the lungs.

Aspiration pneumonia. The acid gastric contents enter the respiratory tract during vomiting, oesophago-gastric reflux and during or soon after anaesthesia. An internist consulting at surgical departments should bear in mind that the currently used endotracheal anaesthesia with obstruction of the trachea simply reduces the incidence and severity of postoperative pneumonia but cannot prevent it in all cases. The vomitus may accumulate proximal to the site of tracheal obstruction and some of it may be aspirated into the respiratory tract after removal of the tube. The gastric contents are also often aspirated into the respiratory tract during epileptic seizures and comas of different aetiology.

The gastric secretions may obstruct the small and sometimes also the medium-sized bronchi, as a result of which pulmonary atelectases develop. Simultaneously with the gastric contents, nasopharyngeal and oesophageal bacterial flora enter the respiratory tract, which facilitates the development of pneumonia. During cough and the attendant deep inhalations, the gastric secretions may enter the small bronchi and bronchioli and induce if not digestion at least acute inflammation of their walls. Experimental data provide grounds to assume that aspirated fluid with pH below 2.5 always leads to acute oedema of the lungs. This condition always develops when the respiratory tract is filled with large amounts

of sea water (e.g. in drowning), ethyl alcohol and other substances producing an irritative effect on the lungs.

A patient, who survives pulmonary oedema, later develops pneumonia, the localization of which is determined by his position during aspiration. In a sitting position (e.g. during tonsillectomy) the lower pulmonary lobes are affected, particularly often on the right side because the right main bronchus is as if continuous with the trachea. In patients confined to their bed, the posterior parts of the upper lobes are often involved besides the lower lobes. In a patient lying on his side during aspiration, only one lung is usually affected. X-ray demonstrates separate or confluent foci of pneumonia. Respiration over the involved areas of the lung is diminished evidently because of pulmonary atelectases. The characteristic change in the percussion note is determined by the size and localization of the inflammatory foci. Neutrophilic leucocytosis with a shift to the left is found in the blood.

The entry into the respiratory tract of small particles of semisolid foods without an admixture of gastric juice leads merely to moderate inflammatory reaction in the lungs. Particles of food or products of its partial digestion are often aspirated in myasthenia, cicatricial strictures, tumours, diverticula and achalasia of the oesophagus, tracheo-oesophageal communications, severe reflux oesophagitis, diaphragmatic hernia, and some other diseases.

The aspirated food particles enter the small bronchi and induce atelectases of the corresponding parts of the lung. These pneumonias have a characteristic localization and a peculiar clinical course. Pneumonia spreads usually to one or more segments either of the lower lobes or of the posterior parts of the upper lobes. The involved lobe is normal or even slightly smaller in volume, which is evidently associated with narrowing of the bronchus supplying it. Physical methods of examination reveal a dull percussion note and rather harsh or diminished respiration with resonant moist rales over the involved pulmonary areas.

The onset of pneumonia is insidious in most cases. A protracted or recurrent course is among its most characteristic signs. The pulmonary infiltration does not tend to resolve rapidly, evidently because the food particles are continuously aspirated. Recurrences of pneumonia of the same or other localization are usually marked by moderate fever and leucocytosis. Microbial flora entering the airways together with the food may cause the formation of a pulmonary abscess. It is characteristic that pulmonary abscesses in these patients also begin insidiously and may not open into the bronchus for a lengthy period of time. In X-ray examination before this happens, the abscess may be mistaken for a tumour of the lung.

It is very difficult at times to establish the diagnosis of chronic pneumonia induced by repeatedly aspirated small amounts of food

It is sometimes misdiagnosed as a malignant tumour, tuberculoma or other diseases in which rounded shadows are demonstrated. The recurrences of pneumonia are sometimes attributed to repeated embolization of the lung from the veins of the pelvis or lower limbs. The diagnostic difficulties arise partly because the patient is unaware that he is aspirating food particles into the trachea. Aspiration of food into the trachea should be presumed in every patient who has an attack of coughing when swallowing. This presumption should be regarded very true to fact in patients with the oesophageal diseases mentioned above and in all patients with disorders of the act of swallowing.

X-ray examination is undertaken to verify this presumption. A barium suspension administered into the pear-shaped sinus of the pharynx through a catheter disappears from the sinus in one or three seconds, but in patients with an impaired act of swallowing it stays there for 30 to 60 minutes. Such examination sometimes reveals a tracheo-oesophageal fistula or the entry of small barium particles into the trachea.

Radiation pneumonia. Ionizing radiation of the pulmonary parenchyma is usually undertaken in metastasis of a malignant tumour to the lungs and after removal of mammary carcinoma. The changes in the lungs develop not during X-ray therapy, but four to six months after it is concluded. Acute radiation pneumonia occurs at first, which terminates in fibrosis.

The inflammatory process begins with necrosis of the endothelium of the pulmonary capillaries. The interalveolar septa thicken because of lymphocytic infiltration and proliferation of immature connective tissue. Cell desquamation and accumulation of effusion occur in the alveoli. The pulmonary parenchyma is replaced by cicatricial tissue in the late stages of the process.

The mildest cases of radiation pneumonia are asymptomatic. Severer cases are marked by dyspnoea which is particularly noticeable on effort. Dyspnoea diminishes markedly but does not disappear completely after the abatement of the acute inflammatory process. More than one third of patients develop a mild dry cough which sharply intensifies on physical exertion and deep breathing. Patients often complain of dysphagia which is attributed to radiation oesophagitis. Body temperature is normal in most cases, though subfebrile fever is sometimes encountered. Physical methods of examination disclose diminished respiratory sounds and foci of fine bubbling rales and crepitation. The ESR is noticeably increased.

X-ray examination demonstrates focal or confluent shadows with a reduced volume of the involved lung. The foci of pneumonia may occur both in the irradiated area and in other parts of the lung. They show no tendency to segmental or lobar distribution. The main and segmental bronchi are not affected in the acute period of the

disease. In later periods the involved lung decreases in volume and consolidates because its parenchyma is replaced by fibrous tissue.

Unresolved Pneumonia

Most virus and bacterial pneumonias end in recovery. According to X-ray control, infiltration of the pulmonary tissue disappears completely in about four weeks after the onset of the disease. It has been suggested that acute pneumonia should be regarded as unresolved if the inflammatory process fails to abate within four weeks. All pulmonary infiltrates which are attended by fever and which do not disappear within four weeks, despite the application of anti-inflammatory therapy, are often mistaken for unresolved pneumonia. By this time the physician is more often confronted with an important diagnostic problem: whether the still existing infiltration in the lungs should be regarded protracted bacterial, mycoplasmal or virus pneumonia, or be referred to the group of allergic or mycobacterial pneumonias or recognized as a syndrome of some other disease. The identification of the aetiology of **unresolved pneumonia** is an extremely difficult diagnostic problem requiring that the physician be capable of synthesizing the results of many methods of examination.

The persistence of pulmonary infiltration may be a consequence of deficient resorption of an inflammatory effusion which had formed in the acute period of the disease (Supplement XXII-1). The infiltrate in the lung may in some cases prove to be another disease, e.g. lymphogranulomatosis, and not pneumonia. The pneumonia syndrome may develop in attendance to some other pulmonary diseases such as tumour of the bronchus. On occasion pneumonia is simply a manifestation of some generalized disease, ornithosis, for instance, or diseases of the cardiovascular or the central nervous systems. It is only natural that long-term pulmonary infiltration combined with a fever of this or that degree, and with shifts in the blood composition is mainly determined in such cases by the character and general patterns of the principal disease.

Most acute pneumonias encountered in internal-disease departments for adults are of pneumococcal or virus origin. Pneumonias caused by staphylococci or Gram-negative bacteria are much less frequent. This order in the frequency of the different causative agents is also maintained in the group of unresolved pneumonias. Pneumococcal pneumonias account for 20 per cent, staphylococcal for 8.6 per cent and mycoplasmal for 2 per cent of all unresolved pneumonias. Unresolved pneumonias induced by Gram-negative bacteria make up 67 per cent.Thus, experience shows that unresolved pneumonia most often proves to be pneumonia caused by bacteria or viruses.

Among the great number of causes delaying the resolution of pneumonia, iatrogenic factors deserve special attention. The introduction of sulphonamides and antibiotics into therapeutic practice brought about a marked decrease in bacterial pneumonia mortality. At the same time, the course of pneumonia changed, pulmonary suppurations and empyema became less frequent occurrences while the incidence of chronic pneumonia went up. Delayed resolution of pneumonias was encountered in 4 per cent of cases before the introduction of sulphonamides and antibiotics into practice, but occurred in 15 per cent of pneumonia cases with their widescale use (Shteingardt and Ageyeva, 1981). The increase in the incidence of slowly resolving pneumonias is explained by the change in the age of the hospitalized patients. Today elderly and aged patients are hospitalized for the most part who are often found to have chronic pulmonary diseases (bronchiectases, pneumosclerosis), diabetes mellitus, arrhythmias or heart failure. The delayed resolution of pneumonia can therefore be partly attributed to the altered reactivity of elderly and aged patients who often suffer from concomitant diseases disturbing the normal drainage function of the bronchi.

The resolution of pneumonias is sometimes delayed by complications which may develop both in the acute period of the disease and in the period of convalescence. Complications which may delay recovery are abscess and atelectases of the lung, empyema, and the formation of sterile effusions in the pleural cavities.

A superinfection with another micro-organism may sometimes delay the resolution of pneumonia. This happens particularly often in patients suffering from severe diseases which either reduce the patient's resistance to infection (multiple myeloma, leukaemias, cachexia due to carcinoma, etc.) or facilitate reinfection of the lungs (impaired swallowing, diseases of the oesophagus, oesophagotracheal fistulae). Superinfection with staphylococci and with Gram-negative bacteria occurs particularly often in patients with pneumococcal pneumonia.

Superinfection should be considered in those cases of pneumonia in which: (1) the prescription of antibiotics at first had led to a fall in body temperature but, after a few days at a normal level, it had risen again; (2) recurrent fever is attended by a rise in leucocytosis and the appearance of new foci of dulled percussion note and bronchial respiration or the appearance of X-ray signs of infiltration in a new lobe or a new segment of the lung; (3) simultaneously with the recurrence of fever and the appearance of new focal shadows in the lungs, there is a change in the microbial flora in the sputum, e.g. the appearance of staphylococcus instead of pneumococcus.

Thus, unresolved pneumonia may be due to the patient's reduced reactivity, the development of clinical complications which are still insufficiently manifest, and to superinfection which may be

both virus and bacterial. In all such cases, we have to deal with pneumonias as with separate nosological entities, each marked by a characteristic morphological substrate and a specific causative agent. After a drug-induced crisis, most patients with unresolved pneumonia have subfebrile body temperature for a lengthy period of time. Short-term 'fever spikes' with increase of body temperature even to 39°C occur at times in patients with normal temperature. The ESR is moderately increased. The blood leucocyte count depends on the activity of the process and ranges from 3500 to 2500 per 1 μl (Silvestrov, 1968). The red blood cell count does not change.

Unresolved pneumonia of bacterial, mycoplasma or virus origin must be differentiated first of all from pneumonia caused by *Mycobacterium tuberculosis* and from pneumonias developing as a complication of pulmonary tumours. A differential diagnosis with pneumonias of other origin (See Supplement XXII-1) has to be made much less frequently. The pulmonary form of lymphogranulomatosis is sometimes misdiagnosed as pneumonia, but unresolved pneumonia must be distinguished most frequently either from pulmonary tumours or tuberculosis.

In tuberculosis, the primary lesion is usually localized subpleurally in the second or sixth pulmonary segment. The entry of *M. tuberculosis* into the alveoli is attended by the appearance in their lumen of a serous or serofibrinous effusion rich in neutrophils. Soon the neutrophils are replaced by macrophages (the precursors of epithelioid cells) which engulf the tuberculosis bacilli. Hypersensitivity to proteins contained in *M. tuberculosis* develops three to eight weeks from the onset of the infection. By this time, granulomas consisting of epithelioid cells, Langhans' giant cells, lymphocytes, and connective tissue form in the lungs. Caseous necroses form in the inflammatory foci under the effect of hypersensitivity. Involvement of the regional lymph nodes in the inflammatory process results in the formation of the 'primary complex'. In some cases it produces only a few symptoms or none at all and is discovered by chance during X-ray examination for some other disease, in others its onset is acute and marked by severe fever and leucocytosis and resembles either virus or bacterial pneumonia. Depending on the height of fever and the changes in the blood and lungs, the primary complex often must be differentiated first from acute and then from unresolved pneumonia.

The advances in the prophylactic trend of Soviet medicine have led to considerable shifts in tuberculosis epidemiology. Today most children are protected from contracting primary tuberculosis which is gradually becoming a disease of late adolescence and young age. In late infection, primary tuberculosis follows an acute course in no more than one third of the patients. In most cases it must be

differentiated from prehilar pneumonia. Caseous pneumonia is now an extremely rare manifestation of tuberculosis. The acute form of miliary tuberculosis is just as rare.

Most forms of secondary tuberculosis begin with an outbreak of an inflammatory process in the region of calcified foci persisting from the period of primary infection. The process is usually marked by periods of abatement and exacerbation. Secondary pulmonary tuberculosis may be acute or chronic. The acute forms of pulmonary tuberculosis disseminated by the haematogenous route resemble lobular virus and mycoplasmal pneumonias in their clinical and X-ray picture. These pneumonias are also marked by an intensified pulmonary pattern and the formation of focal, usually not very dense, shadows in both lungs.

The pulmonary infiltrate consists of a centrally located caseous focus and a zone of productive inflammation surrounding it. Occasional foci may coalesce and form extensive infiltrative-pneumonic lesions of the type of caseous pneumonia and round or cloud-like infiltrates. The round infiltrates are usually asymptomatic, whereas most of the cloud-like infiltrates begin acutely and are at first misdiagnosed as influenza or pneumonia. Caseous pneumonia is now rarely encountered as a complication of pulmonary haemorrhage or as a grave terminal manifestation of the disease.

The data discussed above indicate that infection with *M. tuberculosis* results in pneumonias which must be distinguished from pneumonias caused by other bacteria and viruses. The difference in the methods of treatment lends high practical significance to the problem of their differential diagnosis.

Approximately 50 per cent of cases of pulmonary carcinoma are at first misdiagnosed as pneumonia and it is only after a more or less lengthy and unsuccessful treatment that the diagnosis is reconsidered. According to Uglov (1962), about one third of the patients with carcinoma of the lung are treated for chronic pneumonia for a long time. Errors of an opposite character, when chronic pneumonia is taken for pulmonary carcinoma, often occur too. In about 6 per cent of cases the diagnosis of carcinoma of the lung is changed after thoracotomy to that of unresolved or chronic pneumonia. Pulmonary carcinoma must be differentiated from unresolved pneumonia about as frequently as tuberculosis of the lungs.

In most cases, primary pulmonary carcinoma is of bronchogenic origin. It usually arises from bronchi of the first order and grows peribronchially forming a node close to the hilus of the lung. When carcinoma grows from the bronchi of the second or third order, which is a less frequent occurrence, the shadow of the tumour is located at some distance from the hilus of the lung. The bronchial lumen is always narrowed or even completely obstructed. Necroses often form in the tumour. A cavity forms after the necrotic material

resorbs, which is sometimes mistaken for a tuberculosis cavity or a postpneumonic pulmonary abscess.

Stenosis of the bronchus leads to the formation of atelectasis with the development of pneumonia in the collapsed area, which often suppurates. Pneumonia in bronchogenic carcinoma also develops frequently without atelectasis. Disturbance of the normal drainage function of the bronchus is one of the important causes of its origin. These prehilar pneumonias resolve with difficulty and often undergo carnification. Serous or serohaemorrhagic pleurisy forms if carcinoma grows into the pleura.

Next in frequency comes the form of bronchogenic carcinoma growing not as a node, but along the bronchial wall. It arises in the mucous membrane of a bronchus of the first or second order and spreads both to the periphery of the lung, often reaching the pleura, and in the central direction, surrounding and growing into the wall of the main bronchus and even of the trachea. The wall of the involved bronchus thickens and the lumen is constricted, which is attended by the development of atelectases and pneumonias. Metastatic spread to the bronchopulmonary, bifurcation and mediastinal lymph nodes occurs early in this form of carcinoma.

Carcinoma arising from the alveolar epithelium accounts for only 4.3 per cent of all pulmonary carcinomas. The tumour infiltrates the tissue of the lung. The carcinoma tissue often grows in the alveoli. It spreads from one alveolus to another through pores in the interalveolar septa without destroying the latter. This form of cancer therefore spreads by the same route as pneumococcal pneumonia. Because of this similarity it is sometimes called 'carcinoma pneumonia'. The infiltrative form of carcinoma often occurs in the lower lobes of the lung. Necroses frequently form within the tumour which after resolution leave cavities resembling caverns.

Carcinoma arising from the bronchioles of the lung periphery is usually small. It is distinguished by a tendency to produce extensive metastases to different organs. Its haematogenous metastases in the lungs appear as miliary tubercles indistinguishable from similar tubercles developing in miliary tuberculosis and in diffuse virus pneumonias.

Thus, pneumonias in pulmonary carcinoma may involve a lobe, a segment or part of a segment. They differ in origin and closely resemble bacterial, virus and tuberculous pulmonary lesions in localization and course. The differential diagnosis between these three groups of diseases is very difficult, and because of this the correct diagnosis in some cases is considerably delayed.

Many other diseases of the lungs are also complicated by pneumonias which, developing in atelectatic segments, produce clinical and X-ray signs at times distinguished with great difficulty from those in bacterial and virus pneumonias. Successful differential

diagnosis in such cases to a great measure depends on the internist's and radiologist's skill in identifying the atelectasis syndrome and appraising the specific features of the clinical course of pneumonia in an atelectatic segment.

Atelectasis of a segment or a whole lobe of the lung is often asymptomatic. The appearance of cough, dry or moist rales, chills, and fever indicates that a concomitant infection has developed. The physical signs of atelectasis are commonly known. They include a dull percussion note, diminished respiratory sounds, and vocal fremitus. A small number of moist rales are heard in cases in which air enters a collapsed lobe during inspiration. The severity of cyanosis and dyspnoea is determined by the extent of the collapse. Physical signs cannot be detected in small atelectases and when compensatory emphysema develops around the airless part of the lung. Radiographs demonstrate increased intensity of the shadow of the involved lobe or segment, displacement of the interlobar fissure, elevation of the diaphragm on the involved side, and displacement of the mediastinum to this side.

Quite often the absence of symptoms and the insufficiently manifest X-ray signs of atelectasis compel the physician to pay special attention to the clinical situations which are complicated by stenosis or bronchial obstruction with particular constancy. Atelectasis of a segment or lobe develops particularly frequently in protracted attacks of bronchial asthma. Obstruction usually of small bronchi with mucous plugs is the underlying factor. In severe status asthmaticus, medium-size and even large segmental bronchi are obstructed. Severe compensatory emphysema of the surrounding pulmonary areas makes it difficult to detect the physical signs of atelectasis. The occurrence of fever during an attack of bronchial asthma may be accepted as a reliable sign of developing atelectasis, moreover one that is complicated by infection.

Atelectasis of the lung may also develop in a patient with temporary or permanent tracheostomy. Atelectasis in such cases (as in bronchial asthma) is attributed to bronchial obstruction with mucous plugs.

Atelectases are a particularly frequent occurrence after major operations. During our consultations at surgical departments we often observed them in males who had previously suffered from chronic bronchitis or pneumosclerosis. Prolonged anaesthesia, difficult respiration and expectoration in the postoperative period, and restricted excursions of the diaphragm are conducive to the development of atelectases. They are manifested clinically by fever, tachycardia, and dyspnoea which develop a day or two after the operation and are often misdiagnosed as 'postoperative pneumonia'. X-ray examination often demonstrates disk-like atelectases in the lungs of these patients. Timely application of the appropriate thera-

peutic measures rapidly relieves bronchial obstruction and often prevents the development of pneumonia.

The collective term 'aspiration atelectases' provides for a generalizing description of all atelectases consequent upon stenosis or obstruction of the pulmonary airways by foreign bodies. These atelectases are relatively rare and are mostly encountered in patients with impaired swallowing after operations in the mouth and nasopharynx and in those who are in a comatose state. Aspiration of a foreign body induces an attack of paroxysmal dyspnoea in a patient who is fully conscious. The clinical manifestations of these atelectases are very diverse all the more because they are frequently complicated by pneumonias which usually follow a chronic course. The X-ray diagnosis is only easy in cases where the foreign body is radiocontrast. Knowledge of the case history allows the possible cause of atelectasis to be presumed. In most cases the foreign body can be seen during bronchoscopy.

Persistent atelectases of the lung may be induced by tumours and cicatricial stenoses of the bronchus. They are most commonly encountered in bronchial tuberculosis, pneumosclerosis, bronchiectases and rarely in lymphogranulomatosis and syphilis. Much more frequent occurrences are atelectases caused by compression of the bronchus by adjacent enlarged lymph nodes (in lymphogranulomatosis, sarcoidosis, tuberculosis, metastatic spread of tumours to the mediastinal lymph nodes), tumours of the lungs and mediastinum, pulmonary cysts, aneurysms of the aorta and other arteries, and an enlarged left atrium. With the development of concomitant infection segmental or even lobar pneumonia develops whose true cause may be identified only after the findings of clinical, X-ray and special methods of examination are carefully compared.

For the purpose of simplifying differential diagnosis, four groups of bacterial, virus and other forms of pneumonia arising as an independent pulmonary disease or as a complication of other diseases are distinguished: (1) extensive pneumonias involving a whole lobe or a segment of the lung, i.e. cases in which pneumonic infiltration of the lung can be traced from the root of the lung to its periphery; (2) peripheral pneumonias involving part of one segment or adjacent parts of neighbouring segments; (3) microfocal pneumonias with diffuse involvement of both lungs, one lung or only one of its lobes; (4) prehilar pneumonias which fuse with the pulmonary root and do not spread to the periphery of the lung.

Lobar and Segmental Pneumonias

Bacterial and virus pneumonias may occupy part of or a whole lobe. They may develop within the limits of a single segment or

spread to parts of the neighbouring segments. Simultaneous involvement of both lungs is often encountered; this may be segmental or non-segmental. The difficulties of differential diagnosis may be partly avoided or reduced by separately describing the differential diagnosis of lobar and segmental pneumonias and dividing subsegmental pneumonias into central or prehilar and peripheral forms localized at a distance from the root of the lung.

In many cases bacterial and influenza pneumonias cannot be distinguished one from another by their clinical manifestations. They will be further described under a common title 'bacterial pneumonia'. Mycoplasmal pneumonia can hardly be distinguished from virus pneumonias without using specific methods of examination, so from now on they will be described under the common term 'virus pneumonia'.

Lobar pneumonias are usually of bacterial origin. The severest forms are caused by *Klebsiella* organisms. They usually develop in the upper pulmonary lobe and tend to disintegrate with the formation of cavities if treatment is delayed or inadequate. Staphylococcal pneumonia follows a severe course and is also often complicated by the formation of an abscess. In streptococcal pneumonia signs of pleurisy with effusion are detected in the acute period of the disease. Diplococci are the most common cause of lobar pneumonia, but these pneumonias with the exception of those induced by type III diplococcus are moderately severe.

Confluent lobular pneumonia involving almost the entire lobe is sometimes caused by influenza virus. It is usually encountered during epidemics, takes a very severe course, and terminates in collapse. Confluent lobular pneumonias of mycoplasmal origin are very rare. No marked toxicosis develops. A tendency to take a protracted course is a characteristic feature of these pneumonias. If we add that both bacterial and virus pneumonias are sometimes complicated by atelectases, the main difficulties in making their differential diagnosis become obvious.

Lobar bacterial and virus pneumonias must be differentiated particularly often from **infiltrative-pneumonic forms of pulmonary tuberculosis** and first and foremost from caseous lobar pneumonia which may begin abruptly, resembling bacterial pneumonia, or gradually like secondary bacterial pneumonias developing in attendance to some virus infection. In the past, physicians spent much effort and time to disclose the differences between tuberculous and bacterial pneumonias. They studied the initial manifestations of these diseases and the types of fever in great detail. Unfortunately, contemporary physicians cannot utilize many of these observations for differential diagnosis because of the changes which had occurred in the clinical manifestations of tuberculosis and bacterial pneumonias. The wide-scale use of antibiotics led to a noticeable decrease

in the number of pneumococcal pneumonias and to an increase in pneumonias caused by other bacteria and viruses.

The re-evaluation of differential diagnostic criteria never ceases. It was not so long ago that the prescription of sulphamides and penicillin led to rapid development of drug crisis almost in all cases of acute lobar pneumonia. The absence of such an effect in our times surprises nobody. In our rapidly changing world each generation must elaborate its own diagnostic criteria. Nevertheless, new concepts take root from previously gained knowledge and some signs thoroughly studied by physicians in the past have still not lost their differential diagnostic significance.

The skin of a pneumonia patient stays hot and dry in the febrile period. The patient may have recurrent chills, but perspiration occurs only during a crisis or when an abscess forms. Patients with pulmonary tuberculosis suffer from increased perspiration long before the onset of caseous pneumonia and throughout the disease. Lobar pneumonia is still most commonly caused by diplococci. The sputum in this disease may be mucopurulent with an admixture of blood. Because of its rich glycoprotein content the sputum is always so sticky that it stays glued to the bottom of an overturned spittoon. In tuberculous pneumonia the sputum may contain a small or considerable admixture of blood, but it is not as sticky and never as uniformly impregnated with small air bubbles as the sputum in pneumococcal pneumonia.

In most cases of bacterial pneumonia, toxicosis is very sharply manifest from the first day of the disease. Very many bacteria, the causative agents of the disease, are found in the sputum of these patients. In virus pneumonia there is usually neither severe toxicosis nor many bacteria in the blood. In caseous pneumonia the degree of toxicosis may noticeably differ from one case to another, but the sputum of these patients does not contain many causative agents of pneumonia. Indisposition lasts for days before the onset of bacterial pneumonia and rarely more than a week before virus pneumonia sets in. Indisposition and increased fatiguability for which there seems to be no cause usually appear long before the onset of tuberculous pneumonia.

Most cases of pneumonia begin (like pulmonary tuberculosis) subpleurally. The concomitant pleurisy gives rise to pain which in tuberculosis is usually moderate and localized mostly in the interscapular region in line with the apical segment of the lower and posterior segment of the upper lobe. In bacterial pneumonia, the pain is usually felt in the side in line with the projection of the basal segments of the lower lobe which are involved most frequently. Stimulation of the pleura in both diseases is attended by moderate cough. In virus pneumonia the cough is usually dry, tormenting and attended by retrosternal pain.

The differential diagnostic significance of percussion and auscultation is very limited. Virus pneumonia, like many cases of infiltrative-pneumonic pulmonary tuberculosis, is usually marked by irregular fever, absence of conspicuous changes in the percussion sound, and only a few moist rales. Most cases of bacterial pneumonia are attended by noticeable enlargement of the affected pulmonary lobe. In upper lobar pneumococcal or klebsiella pneumonia, the lower border of the dullness may be determined at the level of the fifth rib in the front and at the level of the spinous process of the sixth vertebra in the back. This differential diagnostic sign is encountered less frequently in recent years, evidently because specific therapy is applied much earlier.

Leucocytosis of over $2 \cdot 10^4$ per 1 μl is found from time to time in the acute period of bacterial pneumonia and almost in all cases of abscess formation and complication by emphysema and sepsis. Leucopenia and moderate leucocytosis are often encountered in tuberculosis and bacterial and virus pneumonias.

Densities revealed by X-ray in bacterial pneumonia may be homogeneous and non-homogeneous. In the latter instance, occasional lobular shadows have no clearly outlined boundaries and gradually merge with the pulmonary tissue. All are of approximately the same duration. The bronchograms are usually demonstrated but in rare cases bacterial pneumonia is complicated by atelectasis and the shadow may then copy the shape of the segment. Tuberculous foci are usually round or oval and more clearly outlined. Besides fresh soft foci, older foci with signs of calcification are usually found in tuberculosis. The appearance of small soft foci on the periphery of the infiltrate and in the contralateral lung is a particularly characteristic sign.

Tomography often demonstrates the beginning of this disintegration already in the early stages of tuberculous pneumonia. The general condition of some patients may even be satisfactory. Bacterial pneumonia may also lead to the formation of a cavity in the lung in the first week of the disease, but this only happens in patients who are in a very grave condition marked by high fever, recurrent chills and high leucocytosis with a shift to the left. The differential diagnosis between a tuberculous cavity and a pulmonary abscess may be made with assurance both at the patient's bedside and by X-ray. Some laboratory tests help in solving this problem and must be made in every case of pneumonia. In differentiating bacterial from tuberculous pneumonia particular significance is attached to examination of the sputum because it is easily obtained and simply prepared for laboratory examination.

The tuberculous aetiology of pneumonia becomes obvious if *M. tuberculosis* are demonstrated in repeated examination of the patient's sputum. If the bacilli are not found in the smear, methods

of concentration are used, among which the floatation method is the simplest. Luminescent microscopy of the sputum is just as simple, but it is as poorly specific as the Ziehl-Neelsen's stain. The other laboratory methods for identifying tuberculous infection in a patient are either insufficiently specific (e.g. complement-fixation reaction) and insufficiently sensitive, or are still inaccessible to most hospitals (e.g. the immunofluorescence method). Bacteriological diagnosis of tuberculosis is used very rarely in clinics for internal diseases because *M. tuberculosis* grows slowly on nutrient media. Methods of biological diagnosis are employed just as rarely.

In the acute period, bacterial pneumonia must be differentiated in most cases from tuberculous pneumonia of about the same extent from the findings of the usual complex of clinical, X-ray and laboratory methods of examination. It is far more difficult to make the differential diagnosis in cases of unresolved pneumonia. It differs from tuberculous pneumonia not as much by its clinical manifestations as by the character of their evolution in time. The use of special laboratory methods may considerably reduce the time required for establishing the final diagnosis in such cases.

Acute pneumonia sometimes resolves very slowly in patients of elderly and old age and in those suffering from diabetes mellitus, bronchiectasis and other debilitating diseases of the internal organs. In some cases, the disease takes a chronic course and then it is spoken of as chronic pneumonia. Klebsiella pneumonia resolves particularly poorly. Sometimes it even takes a progressive course spreading to new segments of the lungs.

Unresolved pneumonia is usually localized in the upper and middle lobes of the right lung and the fourth and fifth segments of the left lung. The volume of the affected segments reduces slightly because of their atelectasis which develops in the acute period of pneumonia. The disease takes a chronic course if the inflammatory infiltrate does not resolve completely. Most patients have pain in the involved side of the chest, cough with a small amount of mucopurulent sputum, and subfebrile body temperature with elevation, from time to time, to 39°C. The acute onset of the disease is evidence of its association with pneumonia.

The clinical picture of the disease described may also develop in **benign and malignant tumours of the bronchus**, which are attended by partial or even total obstruction of its lumen and by atelectasis of the corresponding segment of the lung. Pneumonia in an atelectatic segment or lobe differs from ordinary bacterial pneumonias in the character of their further course and not in the clinical manifestations. In some cases, it is resistant to chemotherapeutic agents and takes a protracted course from the beginning. In others it tends to recur. A short time after the first pneumonia resolves,

acute pneumonia again develops in the same lobe. The clinical picture of unresolved and recurrent pneumonias is often caused by the same disease, namely, bronchial tumour.

Specialists in pulmonary surgery claim that internists make the diagnosis of pulmonary carcinoma in far-advanced stages, as a rule, when pulmonary and remote metastases are already present. The delayed diagnosis of carcinoma of the lung is mainly explained by the insufficient awareness of the internists that this might well be an oncological case. They spend too much time treating patients from chronic pneumonia and send them belatedly to oncological institutions for consultation. Any unresolved pneumonia, particularly in the elderly and aged, should be regarded as a possible complication of carcinoma and should become the subject of special examinations, bronchoscopy, bronchography and tomography in particular. Cytological examination of the sputum may reveal many bacteria both in pneumonia and in bronchial carcinoma. The results of cytologic examination of washings from the bronchial mucosa are of undoubted diagnostic value. When carried out by skilled cytologists this method yields the correct diagnosis of bronchial carcinoma in 60 to 90 per cent of cases. Fraser and Parre (1970) claim that cytological examination of sputum or washings from the bronchial mucosa supply more diagnostic information than bronchoscopy.

Bronchoscopy in combination with spot biopsy of the mucous membrane (whenever necessary) is considered indicated for every patient in whom bronchial carcinoma is suspected, i.e. for all patients with unresolved pneumonia. The value of the examination depends on the location of the tumour. About 80 per cent of carcinomas in the lobar and segmental bronchi may be diagnosed by means of bronchoscopy. Its value is somewhat lower in tumours of smaller bronchi. Tomography of the lungs reveals separate tumour nodules, demonstrates disintegration cavities in them and deposits of calcium salts invisible on ordinary radiographs. The method also permits assessment of the size of some mediastinal lymph nodes and in this way settles the question of metastases and, consequently, of the cause of chronic pneumonia. The patency of large bronchi may be judged from the tomograms, but partial and even total obstruction is encountered both in tumours and in chronic pneumonias.

Some of the difficulties that are pointed out are overcome by applying bronchography. Some authors emphasize that in chronic pneumonia the bronchi are not obstructed and sacculated or cylindric bronchiectases are found in them. In total obstruction of the bronchus, its stump in chronic pneumonia is always long, reaching 2 cm at times. In carcinoma bronchiectases are not found, and the bronchial stump is always short and located at the very orifice. If these methods fail to disperse diagnostic doubts, it is recommend-

ed to transfer the patient to a surgical department for exploratory thoracotomy.

Alveolar carcinoma of the lung may be asymptomatic for a considerable length of time. In later stages it is attended by fever, cough, dyspnoea and chest pain. Blood tests often show leucocytosis and increased ESR. Not one but usually several spherical shadows are seen in the lung in such cases. These shadows may occupy a whole lobe, one or even both lungs. They often coalesce and create the impression of confluent acute bronchopneumonia. Occasional tumour nodules may disintegrate increasing the resemblance with pneumonia complicated by the formation of an abscess.

Antibiotic and sulphanilamide therapy is ineffective in such cases. Fever, cough with sputum, and the shadows in the lung do not disappear completely and sometimes even become more manifest despite continuing therapy. Other methods must be resorted to for identifying the cause of the disease. Bronchoscopy usually proves futile because the tumour is localized in the small bronchi. Cytological examination of the sputum and tomography are very valuable. The latter may also prove valuable for detecting the beginning of disintegration in occasional nodules.

Adenoma of a bronchus is a rare disease. The tumour arises from the components of the bronchial wall and remains within the limits of the bronchus for good or at least for a long time. Two types of adenomas are currently distinguished: carcinoid tumour and cylindro-adenomas. The carcinoid tumour usually grows externally from the bronchial wall and only a small part of it protrudes into the bronchus in the form of a polyp. The surface of the tumour is covered with normal epithelium. Cylindro-adenomas usually infiltrate the bronchial wall and grow externally, often producing metastases to the regional lymph nodes and sometimes to the liver and other organs. About 80 per cent of all adenomas are lodged in the main bronchi and about 10 per cent in bronchi of the second order. Central localization of adenomas makes their diagnosis much easier by bronchoscopy.

The clinical manifestations of bronchial adenomas comprise signs caused by the effect of the tumour itself on the bronchial wall and signs developing under the effect of secondary infection. Pneumonia is a late complication of adenoma. It always develops in an atelectatic segment of the lung. Its initial clinical manifestations are to a great measure determined by the character of the causative agent and may in no way differ from the initial manifestations of other pneumonias. Two specific features distinguish this pneumonia from acute pneumonias of bacterial or virus origin. Pneumonia in a patient with bronchial adenoma tends to take a protracted course or recur. It begins not in full health, but in a patient with a pulmonary disease of some duration.

Pneumonia in an atelectatic pulmonary segment always shows a tendency to take a protracted course. The pneumonic infiltrate either does not resolve at all or resolves with considerable delay. Its protracted course is often explained by the formation of an abscess which naturally sharply retards the patient's recovery. A recurrence of pneumonia in the same segment should also be considered as an indication of the need a more thorough bronchologic examination.

High differential diagnostic significance should be attached to the patient's condition before the onset of pneumonia. Patients with bronchial adenoma always have a persistent cough sometimes with expectoration of a small amount of blood long before the acute disease begins. Dry or moist rales were often heard before the onset of pneumonia in these patients. These rales are caused by atelectasis of one of the pulmonary segments and are sometimes mistaken for manifestations of chronic bronchitis or bronchiectases.

Because of cough and additional respiratory sounds, which are heard for a long time, the patient is often subject to various types of examination. Thus, the medical history and observation over the course of pneumonia in bronchial adenoma allow it to be distinguished from acute bacterial or virus pneumonia in an otherwise healthy person. These differences are enough reason for a more detailed diagnostic study of the patient, which is composed of cytological examination of the sputum, bronchoscopy, bronchography and tomography.

After the pneumonia resolves, bronchial adenoma may be discovered in the root of the lung as a spherical shadow with clear, at times irregular outlines. Tomograms demonstrate a homogeneous shadow sometimes with foci of calcification in it. A tomogram also shows narrowing of the bronchus draining the atelectatic segment of the lung. Calcification inside the tumour is evidence of its benign character.

Most bronchial adenomas are covered with normal epithelium, and cytological examination of the sputum therefore cannot help in identifying the cause of the unusual course of pneumonia. About 84-90 per cent of all adenomas in bronchi of the first and second orders can be seen during bronchoscopy. Tumours in smaller bronchi can be detected by bronchography.

Delayed resolution of aspiration pneumonia is often attributed to repeated aspiration of food particles due to the continuing action of factors impairing swallowing. The location of these pneumonias depends on the patient's position during aspiration. Persistent hypereosinophilia allows Loeffler's syndrome to be easily distinguished from unresolved pneumonia of bacterial or virus origin.

Changes in the lungs in **lymphogranulomatosis** usually appear after one of the exacerbations of the process in individuals suffering

from a lesion of the mediastinal lymph nodes for a lengthy period of time. Sometimes these changes are an unexpected finding during X-ray examination. Primary involvement of the lung in lymphogranulomatosis is very rare. Invasion of the bronchial submucosa by specific tissue of the lymphatics leads first to stenosis of the bronchus and later to blocking of its lumen. Infection of an atelectatic segment or lobe is attended by pneumonia. In some cases, pneumonia may be the earliest pulmonary manifestation of lymphogranulomatosis and predominate in the clinical picture of the disease.

In practice, this pneumonia must be differentiated from ordinary bacterial pneumonia. The results of physical methods of examination are usually identical. The medical history, the findings of bacterioscopy and X-ray, and the specific features of the course of the disease may serve as the guiding point in the differential diagnosis of these pneumonias.

Fever is one of the signs of generalization in pulmonary lymphogranulomatosis. Antibiotic therapy may lead to the disappearance of toxicosis caused by pneumonia, but does not relieve fever. Infiltration of the pulmonary tissue remains despite adequate antibiotic therapy. The volume of the involved lobe or segment in lymphogranulomatosis, like in pneumonia, does not decrease, but, as pointed out above, in pneumonia the bronchogram is demonstrated, whereas in lymphogranulomatosis the bronchus is obstructed. These differences are best illustrated on tomograms. The cause of pneumonia becomes obvious when extrapulmonary signs of lymphogranulomatosis are found.

Lobular Pneumonia

The term 'lobular pneumonia' designates solitary or multiple inflammatory foci involving several lobules of one or both lungs. Although lobular pneumonias differ from lobar and segmental pneumonias mainly in the size and number of foci, their grouping in a separate chapter is expedient because of the frequently arising difficulties in identifying their aetiology.

Lobular pneumonia is evidently the disease most commonly encountered by the internist in the winter, spring and autumn seasons. The wide-scale introduction of large-frame fluorography revealed that lobular pneumonias should be regarded as the most frequent complications of acute respiratory diseases. Long-term study of the evolution of these pneumonias noticeably improved the diagnosis of many other pulmonary diseases.

The onset of the disease may be either abrupt or insidious. One or usually more foci of inflammation are discovered in the lungs. Bacterial lobular pneumonias commonly set in abruptly and are

marked by the formation of a few or many inflammatory foci. Solitary foci are very rare in bacterial infection. Virus infection may occur with the formation of one or more inflammatory foci in the lungs. The considerable variety in the severity of the disease and the character of developing complications is explained by the diversity of its causative agents and the different initial condition of the patient by the time the disease develops.

Some virus pneumonias (e.g. adenovirus induced pneumonia) may be asymptomatic and are discovered accidentally during X-ray examination for a disease which is seemingly a mild case of catarrh of the upper respiratory tract. In a few days or weeks, these pneumonic foci disappear without a trace in most cases, but in occasional patients they show no tendency to resolve. The foci of such protracted pneumonia usually acquire a spherical shape. They are found in the upper and lower lobes of the lung with equal frequency. According to Vinner and Shulutko (1971) such spherical pneumonias account for 7.6 per cent of all chronic pneumonias and for up to 4 per cent of all other spherical structures in the lungs. On the radiographs they are seen as spherical shadows whose blurred contours gradually dissolve in the pulmonary tissue.

An insidious onset is characteristic of most virus and of some bacterial pneumonias. Pneumonias caused by Gram-negative bacteria follow an especially peculiar course. Proteus-induced lobular pneumonia always begins insidiously and is marked by moderate fever and mild leucocytosis but it terminates in the formation of an abscess, as a rule. Lobular pneumonia caused by Pfeiffer's bacillus begins abruptly in most cases; it is marked by high fever but its outcome is favourable. Lobular pneumonias caused by *Escherichia coli* are localized in the lower lobes of the lung.

The findings of physical examination are determined by the location of the foci. Pneumonias caused by Proteus and diplococci are located subpleurally, which makes their diagnosis much easier. The pulmonary airways in virus lobular pneumonias are often intact and it is therefore difficult to reveal them by physical examination. Only a small number of moist rales may be heard on inspiration in rare cases. The X-ray method would be indispensable in the diagnosis of lobular pneumonias if it were not for the great number of other diseases which likewise develop with the formation of one or more focal shadows in the lungs.

Information gained from the medical history, including epidemiological data, and the findings of physical examination allow a tentative diagnosis of lobular pneumonia to be made. It is desirable that this diagnosis be verified by bacteriological or serological tests. The final diagnosis of lobular pneumonia may only be established retrospectively, i.e. after all clinical signs disappear and the infiltrate in the lung resolves completely under the effect of treat-

ment. The diagnostic importance of repeated blood tests should also not be overestimated. They neither confirm nor rule out the diagnosis of bacterial or virus lobular pneumonia, but are absolutely indispensable in differentiating it from other lobular lesions of the lung.

In departments for internal diseases at town hospitals lobular pneumonia of bacterial or virus origin must be differentiated most frequently from infarction, tuberculosis and alveolar carcinoma of the lung. Less frequently a differential diagnosis must be made between bacterial or virus lobular pneumonia and other pulmonary diseases listed in Supplement XXII-1.

Pulmonary thromboembolism is a quite frequent terminal complication developing in serious cases at departments for internal and nervous diseases at town hospitals. Thromboembolism of large branches of the pulmonary artery usually terminates in sudden death and is therefore rarely diagnosed while the patient is alive. Thromboembolism of small arteries may be asymptomatic and may give rise to indefinite complaints the true cause of which becomes evident only retrospectively. Between these two extremes are thromboembolisms of medium-sized arteries; they lead to the development of infarction of the lung which is often mistaken for pneumonia or for myocardial infarction complicated by pneumonia.

The diverse clinical manifestations of pulmonary infarction develop under the effect of involvement of the lung itself and of concomitant disorders in the cardiovascular system. Pulmonary infarction always begins with dyspnoea which may be the only symptom of the disease in cases of small thromboembolisms. Short-term dyspnoea sometimes heralds larger thromboembolism terminating in pulmonary infarction. In some cases, dyspnoea develops to the extent of paroxysmal dyspnoea during which many dry and a small number of fine-bubbling moist rales are heard in both lungs. Approximately 50 per cent of patients experience chest pain, sometimes retrosternal, at other times in the side or back, during the attack of paroxysmal dyspnoea. In clinical manifestations retrosternal pain does not differ from similar pain in myocardial infarction. Pain in the side is explained by stimulation of pleura adjoining the pulmonary segment involved in the infarction.

Depending on the size of the thrombosed vessels, all these symptoms may be moderate or sharply manifested. Paroxysmal dyspnoea may lead to diffuse cyanosis or it may subside to moderate dyspnoea. Haemoptysis occurs in about a third of the patients who survive the acute period of the disease. With the development of peri-infarction pneumonia, fever and moderate leucocytosis appear. In most patients physical examination reveals a dull percussion note, usually over the posterior basal segment of one of the lungs, the pleural rub, a small number of dry and moist rales and diminished

respiration. Accumulation of fluid in the pleural cavity of the involved side is often found a few days later.

Thromboembolism of several segmental arteries is marked by the development of pulmonary hypertension which, in turn, leads to the development of the acute cor pulmonale syndrome. Its clinical signs are as follows: pulsation of the right ventricle of the heart in the 3rd-4th intercostal space at the right sternal edge, accentuation of the second sound over the pulmonary artery, Graham Steell's diastolic murmur, and pulsation of the pulmonary artery in the second right intercostal space. It should be emphasized that these signs are detected only in a case of extensive embolism of the pulmonary artery. In cases of pulmonary infarction which must be differentiated from pneumonia, these signs are usually mild.

The electrocardiographic signs of acute cor pulmonale also appear in thromboembolisms complicated by pulmonary hypertension. The electric ECG axis is turned to the right, S wave is depressed in lead I, and a deep Q wave appears in lead III. At the same time, the configuration of the ST-T complex changes in lead III and wave T_{III} becomes negative. Signs of right-atrial hypertrophy sometimes appear. These changes last one to three days and to detect them it is therefore necessary to record the ECG in the first days of the disease. In thromboembolism of the segmental branches of the pulmonary artery the ECG may be normal or simply a short-term T wave inversion is recorded in leads I-II-III.

Pulmonary infarction often develops in patients bedridden for a long time, in those with thrombophlebitis of the legs and pelvis, in patients with cardiac fibrillation and signs of heart failure, and in obese persons. The incidence of thromboembolisms of the pulmonary artery has grown in recent years among young females taking contraceptives which contain oestrogens.

X-ray examination in pulmonary infarction demonstrates a density and decreased volume of one of the segments, mostly the posterior basal segment. Elevation of the diaphragm on the involved side is found in approximately a third of cases. An infarct extending only to one pulmonary segment is seen as a homogeneous dense triangle. Its base faces the visceral pleura, while the apex is directed at the hilus of the lung. In multiple infarcts, this classical form disappears. In some cases, a pulmonary infarct is demonstrated as a linear horizontal shadow stretching 1 or 3 cm above the diaphragm. The size of the infarct determines the rate at which its shadow disappears. If no complications develop (pleurisy with effusion or disintegration) the density produced by the infarct disappears in one to three weeks.

The possibilities for establishing the diagnosis of pulmonary infarction improved noticeably with the introduction into clinical

practice of lung scanning with ^{131}I-, ^{51}Cr- or ^{99m}Tc-labelled albumin macro-aggregates.

Ischaemic areas ('cold zones') are demonstrated on the scanograms of the lung; in location they correspond to the segments involved in the infarction. Repeated scanning makes it possible to watch the restoration of the blood flow in the involved lung or to discover the formation of new infarcts.

Pulmonary infarcts are located in the lower lobes, as a rule. The pleural rub and a serohaemorrhagic effusion may appear when the patient's condition is satisfactory. The pleural rub is heard only in severe lobar pleuropneumonias. Pleurisy with effusion in pneumonia is always purulent or seropurulent, and occurs only in cases of very severe pneumonia. The volume of the involved segment increases in pneumonias caused by the most widespread Gram-positive bacteria, but decreases in pulmonary infarction. Infarcts are almost always located in the lower lobes whereas pneumonias often develop also in the upper lobes.

As it is said above, lobar and segmental pneumonias must be differentiated from infiltrated pneumonic tuberculosis occurring as lobitis, caseous pneumonia and cloud-like infiltrate involving one or more segments of the lung. In addition, the internist is often obliged to make the differential diagnosis between bacterial or virus lobular pneumonia and a **primary tuberculous complex** and **reinfection with pulmonary tuberculosis** in adults. In late primary infection the pneumonic focus in the lungs is restricted in size and forms subpleurally. Its clinical course is distinguished by immense diversity. In most adults it has no marked clinical manifestations. About one third of patients seek medical advice for the first time because of a febrile disease which they think had developed abruptly in them, and which can be misdiagnosed as lobular pneumonia.

An outbreak of perifocal inflammation around an old tuberculous focus is sometimes also mistaken at first for an acute respiratory disease because their clinical manifestations are often almost identical (Rubinshtein, 1949). In a few days the patient's condition improves and body temperature drops to normal levels. After a period of relative well-being of various duration, the condition is again aggravated. Cough continues and is usually neither intensive nor frequent. Sputum is expectorated in small amounts or not at all. Dry cough is always encountered in virus pneumonias. In the acute period of the disease it is frequent and troubles the patient. With the passage of time from the onset of the disease, the cough becomes softer and small amounts of sputum are expectorated. Cough is always observed in unresolved bacterial pneumonia too.

The findings of physical examination also fail to provide sufficiently reliable grounds for the differential diagnosis of these diseases. A dulled percussion note is found only in cases of a very large

infiltrative focus or in fusion of several small foci located close to the pleura. Foci of bacterial pneumonia are usually larger than the tuberculous foci and may therefore be sometimes localized from the results of percussion. Bacterial pneumonia is marked by affection of the pulmonary airways. That is why its foci are often discovered by the presence of moist rales on auscultation. Foci of virus pneumonia, just as foci of tuberculosis, form in the stroma of the lung and are therefore usually not revealed by auscultation, although their existence is easily demonstrated by X-ray.

In most cases of pulmonary tuberculosis, toxicosis is less marked than in bacterial pneumonia, but it is essential to emphasize that toxicosis is also mild in some virus pneumonias and in pneumonias caused by Pfeiffer's bacillus and *Proteus vulgaris*. Subfebrile body temperature, moderate leucocytosis or a normal blood leucocyte count as well as increased ESR are equally characteristic both of pulmonary tuberculosis and of unresolved pneumonia of bacterial or virus origin. These signs may also be encountered in carcinoma of the lung because necrosis forms inside the tumour.

The medical history and the results of physical examination possess no independent differential diagnostic value. Lobular bacterial pneumonia is most prevalent among the diseases compared here. That is why any deviation from its typical clinical course as well as any not too obvious complication of an acute respiratory disease should be regarded an indication for most thorough examination of the patient (X-ray first and foremost) without delay. Most of these patients are found to have a spherical shadow whose origin is determined only by means of special methods of examination.

In appraising the results of radiography, it should be borne in mind that a pulmonary focus of the primary tuberculous complex is localized subpleurally, mostly in the first or second segment of the lung. This is usually the site of an outbreak of inflammation around old tuberculous foci in adults and also the site of the initial node of alveolar carcinoma of the lung and the most common site of inflammatory foci in any bronchogenic infection. The localization of the shadows acquires high differential diagnostic value only in association with the dynamics of changes in the clinical manifestations of the disease. Unfortunately, we often have no right to follow the natural course of the disease too long because the time for applying effective therapy may be lost.

The spherical shadow of a tuberculous infiltrate may be soft and unclearly demarcated from the surrounding pulmonary tissue. Exactly the same properties may be found in spherical foci of chronic pneumonia. The tendency to disintegrate is typical of both diseases, but it is stronger in tuberculosis than in pneumonia. Tuberculous infiltrates are unilateral, as a rule. Foci of unresolved

pneumonia are also unilateral in most cases. A 'path' to the root of the lung appears at the beginning of disintegration of a tuberculous infiltrate. Small fresh foci of tuberculosis are often seen around infiltrate and along the path. Such foci occur neither in bacterial nor in virus pneumonia.

Denser, well-outlined foci, at times with traces of calcification, may be found besides the soft foci around the infiltrate. These signs are not encountered in pneumonia and are very rare in alveolar carcinoma. The difference in the density of the foci as well as the phenomena of disintegration and calcification are demonstrated most easily on tomograms. Fistulae in the bronchial walls, characteristic of tuberculosis, are sometimes found by bronchoscopy. Enlargement of the lymph nodes in the root of the lung is a constant sign of the primary tuberculous complex and is practically not encountered in reinfections. The results of tuberculin tests are also of high differential diagnostic value. An intense tuberculin reaction is evidence of tuberculous inflammation of the lungs. 'Turning' of the tuberculin tests is of particularly high diagnostic significance.

Pneumonias and tuberculous infiltrates undoubtedly differ in the rate of their resolution, but this feature cannot be applied in solving this diagnostic problem just in one patient. The problem of the differential diagnosis arises only in cases of unresolved pneumonia, i.e. precisely in those instances which are similar to tuberculosis in this parameter of the clinical course. In the long run, the diagnosis must be verified by the discovery of *M. tuberculosis*. All the possibilities including bacterioscopic, bacteriologic and biological methods of examination must be used to this end. The search for *M. tuberculosis* in unresolved bacterial and virus pneumonias proves futile.

Particular caution must be exercised in appraising the results of trial treatment of tuberculosis with modern chemotherapeutic agents. Rubinshtein (1949) points to the possibility of spontaneous rapid disappearance of a tuberculous infiltrate.

Bronchiolar (alveolar) carcinoma of the lung in some cases resembles lobular pneumococcal pneumonia in its clinical manifestations. The tumour usually occupies part of a segment. In about half of the patients it is asymptomatic and is a chance find during prophylactic examination or during control X-ray after recovery from an acute respiratory disease. For a long period of time the tumour shows no tendency for aggressive growth. A dry cough appears when the tumour begins to grow, later the cough becomes productive. The sputum is usually mucous. This is followed by fever and signs of stenosis of one of the bronchi. Pneumonia often develops in the atelectatic segment. Pain in the chest and pain during respiration indicate that the tumour is spreading towards the pleura. Haemoptysis and dyspnoea develop in the later stages of the disease.

X-ray reveals a homogeneous, usually spherical shadow with clear edges. In infiltrative growth of the tumour its outlines may blend with the surrounding pulmonary tissue. The tumour is localized peripherally and its diameter ranges between 1 and 6 cm. In some cases, the tumour consists of many small foci which coalesce and may extend to part of the lobe. The lymph nodes in the root of the lung are normal or enlarged. In combination with fever and leucocytosis a picture resembling confluent lobular pneumonia may develop.

Tomography makes it possible to study the structure and contours of the tumour and determine the patency of the lobar bronchi. Examination of bronchograms shows that the tumour arises mostly from the bronchi of the fourth or fifth order. Contrast study demonstrates signs of extension of the tumour into the bronchi in most cases (narrowing of the bronchi, a bronchial stump, arrest of the contrast medium at the edge of the tumour). In protracted and chronic pneumonia, bronchography demonstrates bronchiectases in the afferent bronchus. These are not found in cases of alveolar carcinoma. A neglected tumour disintegrates from the inside with the formation of a cavity in it which is usually visible on the tomogram. Alveolar carcinoma of the lungs sometimes leads to the development of the hypertrophic osteoarthropathy syndrome which is encountered neither in acute pneumonia nor in pulmonary tuberculosis.

Adenoma arising from the peripheral bronchus. Recurrent and unresolved pneumonia sometimes proves to be a complication of adenomas arising from subsegmental bronchi. These tumours, like alveolar carcinoma of the lung, are asymptomatic for a long time. Cough and moderate haemoptysis (in about half the cases) appear later. Pneumonia is a late complication of the tumour. It is associated with infection of atelectatic segments of the lung. The recurrence of pneumonia is usually explained by periodical aggravation in the ventilation of the pulmonary segment because of the growth of the tumour. The bronchus is obstructed in the late stages. Lobular pneumonias in an atelectatic area of the lung follow a protracted course, often with the formation of an abscess.

Adenomas of a peripheral bronchus are demonstrated on radiographs and tomograms as a spherical (usually homogeneous) shadow at times with calcium inclusions. A bronchogram shows that the small bronchi are moved apart by the tumour and that the contrast medium had not passed into the involved bronchus. Chronic pulmonary inflammation is often attended by atelectasis, but the bronchi in the inflamed part of the lung are not obstructed. Like alveolar carcinoma of the lung, adenoma grows very slowly. It is usually encountered in patients under the age of 40, whereas the age of most patients with carcinoma of the bronchus is over 40. Adenomas are mainly found in the upper and middle lobes of the

right and in the lingula (4th and 5th segments) of the left lung.

Bronchial adenoma is always seen as a solitary tumour. Small focal shadows are never seen around it, in distinction from a tuberculous infiltrate. It differs from pneumonia in well-defined outer contours and resistance to antibiotic therapy. A path of lymphatic vessels stretching from the medial side of the tumour to the root of the lung is seen in the late stages of alveolar carcinoma. The root of the lungs may be normal in such cases or contain enlarged lymph nodes. The absence of a path distinguishes bronchial adenoma from alveolar carcinoma and tuberculosis of the lungs.

In rare cases, spherical shadows in the lungs are produced by other benign tumours of the bronchi, e.g. lipomas (usually growing endobronchially and causing obstructive pneumonia), hamartomas (which mostly grow outwards from the bronchus), fibromas, neurofibromas and leiomyomas. They follow a subclinical or asymptomatic course for a great length of time. Pneumonia joins these tumours only in the late stages of their development. It is a consequence of infection in the atelectatic segment of the lung. Whether the tumour is malignant or benign may often be determined only after exploratory thoracotomy.

Tuberculoma (caseoma of the lung) usually develops from other forms of tuberculosis. It consists of one or more (usually coalescent) spherical structures more than 1 cm in diameter. In most cases treated with antibacterial agents it is asymptomatic. In rare cases elevated body temperature, night sweating, chest pain, and cough, either dry or with a small amount of sputum, are noted. Pulmonary tuberculoma is very poor in clinical symptoms and the diagnosis may be made only by X-ray examination.

Tuberculoma is mostly localized subpleurally in the upper lobe. Its shadow may be homogeneous or non-homogeneous. A disintegration cavity is sometimes seen in it. The contours of the cavity are usually clearly defined. They become blurred when perifocal inflammation develops. In some cases it may be mistaken for lobular pneumonia. Tuberculous foci are found around the tuberculoma in most cases. This happens neither in bacterial nor in virus pneumonias. The diagnosis of tuberculoma presents no difficulty in most patients. Tomography is most valuable.

Lymphogranulomatosis of the lungs. Specific granuloma in primary pulmonary lymphogranulomatosis arises in the bronchial wall. With growth it invades the depths of the pulmonary tissue, but the lymph nodes of the mediastinum and roots of the lungs may not be affected. Foci of such 'granulomatous pneumonia' may exist in isolation for some time. Several foci sometimes occur; they coalesce and form a polycyclic tumour. Fever, leucocytosis and cough add to the similarity with peripheral lobular pneumonia. The differential diagnosis between these diseases may be very dif-

ficult. The absence of a causative agent of pneumonia in the sputum, the clearly demarcated peripheral contours of the shadow of the lung, the inefficacy of antibiotic therapy, and the tendency of the tumour to growth despite treatment distinguishes pulmonary granuloma from pneumonia. The final diagnosis is established by identifying extrapulmonary signs of lymphogranulomatosis.

Lymphosarcoma. It has been noted that patients with primary sarcomas of the lungs are often sent to the clinic with a tentative diagnosis of pneumonia. In endobronchial growth, even a small tumour causes stenosis of the bronchus. Infection of an atelectatic segment or lobule leads to pneumonia. Primary sarcoma may arise in the pulmonary parenchyma. Later it may grow into the bronchus or displace it. Pneumonia proves to be one of the syndromes of lymphosarcoma. The other signs are: fever, pain in the chest, dyspnoea, and haemoptysis.

Fever develops in the early stages of the disease, haemoptysis occurs only at the end. Lymphosarcoma prevails among young persons. X-ray demonstrates a spherical or oval well-defined tumour in the early stages of the disease. Pneumonia and dyspnoea appear in the later stages. The tumour grows extremely rapidly and produces early metastases to the cervical and mediastinal lymph nodes and the pleura.

Diffuse Miliary Pneumonias

Acute pneumonias induced by viruses and bacteria are sometimes marked by the formation of miliary foci of pulmonary tissue infiltration which in some cases are spread uniformly in both lungs while in others they form within the limits of one lung or one or two lobes of a lung. Besides miliary shadows, a reticular structure is often demonstrated on the radiographs, particularly in cases of virus pneumonias. The clinical picture of these pneumonias has no features distinguishing them from macrofocal or confluent pneumonia. Diffuse miliary pneumonias are particularly often caused by adenoviruses, *Mycoplasma pneumoniae*, staphylococci, streptococci, klebsiella and, less frequently by diplococci.

Despite the small dimensions of the infiltration foci in the pulmonary tissue, these pneumonias may take a protracted course. Protracted fever combined with characteristic shadows in the lungs causes considerable diagnostic difficulties. Over a hundred diseases may be marked by moderate or high fever with cough, dyspnoea and miliary shadows in the lungs. Separate lobular and acinic foci are superimposed on the radiographs, forming confluent 'bronchopneumonic' shadows in places. In the internist's practice, miliary pneumonias must be differentiated most frequently from pulmonary

tuberculosis, miliary carcinomatosis, left-ventricular failure and occupational diseases.

It is most difficult to make the differential diagnosis between miliary pneumonias and **haematogenic-disseminated forms of pulmonary tuberculosis**, because they are marked by fever, expectoration of small amounts of sputum and toxicosis. There can be no doubt that toxicosis is more intensive in bacterial pneumonias than in tuberculosis, but, besides bacterial, virus miliary pneumonias also exist in which signs of toxicosis are mild. Study of the medical history yields in some cases differential diagnostic criteria which are more reliable. Bacterial and virus pneumonias are acute diseases. Some patients with tuberculosis of the lungs assert that they had fallen ill abruptly while in full health. Detailed questioning, however, brings out that the patient had been suffering from cough for quite a while, sweats at night, his body temperature rises slightly time and again and that in the last three or four weeks he had been getting very tired from work which formerly had not caused fatigue.

The different sensitivity of patients to tuberculin is a good differential diagnostic sign in some cases. Tuberculin reactions are negative or weakly positive in patients with pneumonia but are usually sharply positive in those with tuberculosis.

Miliary pneumonia often involves only one pulmonary lobe sometimes only the lower one, whereas pulmonary tuberculosis disseminated by the haematogenous route is almost always bilateral. 'Exceptions are very rare here' (Rubinshtein) and the formation of small foci in one lung is therefore evidence against a tuberculous process.

Focal shadows in miliary pneumonia are usually not intensive they are unclearly demarcated and always differ noticeably in size In a diffuse bilateral process the upper lobes are usually involved less intensively than the lower lobes. All focal shadows are of equal density because they had developed at the same time. Tuberculous foci are heterogeneous on the radiograph. Besides soft foci in adult there are denser and quite often old calcified foci which are best demonstrated on tomograms.

The pulmonary X-ray signs of miliary pneumonia are quite variable. They usually resolve after some time without a trace (Croton and Douglas, 1971). Resolution of the foci in one or three months is an extremely rare occurrence in tuberculous eruption. Rubinshtein claims that 'focal changes in tuberculosis are often complicated by disintegration, whereas resorption of perifocal inflammation leaves indurative changes often with dense and petrified foci Foci of bacterial and virus pneumonia which remain unresolved for a long time or give rise to chronic pneumonia nevertheless do not undergo calcification. Bacterioscopic and bacteriological exam

ination of the sputum may be of decisive help in making the differential diagnosis of these diseases.

Modern chemotherapeutic agents are often used both for therapeutic and diagnostic purposes. In principle, microbiological diagnosis is required when antimicrobial therapy is prescribed. At the same time, antibiotics, particularly those possessing bactericidal properties, are often prescribed for patients empirically before the examination has been concluded. Such urgency of specific treatment prevents early bacteraemia and endotoxaemia, and sometimes septic shock, and may save the patient's life. Such tactics are considered obligatory when bacterial pneumonia is suspected. A course of treatment with tuberculostatic agents is given in cases of suspected tuberculosis.

Miliary carcinosis. Bronchogenic ('small') carcinoma of the lung, carcinoma of the cardial part of the stomach, and, in rarer cases, carcinoma metastatic spread from other organs, also produce micromacular pattern in one or both lungs as in pneumonia. In combination with more or less marked fever, leucocytosis and increased ESR, this picture is sometimes mistaken for pneumonia.

Knowledge of the patient's age and previously suffered diseases sometimes make the differential diagnosis of these diseases easier. The possibility of carcinoma with metastasis may be considered in patients over 40 years of age. Information on some chronic disease of the lungs, stomach or some other organ may sometimes be found in the medical history. It is important to find out whether the patient had been subjected to X-ray therapy after an operation, e.g. after removal of the ovaries or mammary gland.

The patient's appearance in these diseases is also of differential diagnostic significance. Miliary carcinosis is a late complication of carcinoma. The skin of these patients is earthen grey. Rapid development of weakness and dyspnoea is particularly striking. Trial antibiotic therapy proves ineffective. Simultaneous dissemination in the lungs, pleura and pericardium is often encountered. Pleural effusion may be serous at first, but becomes serohaemorrhagic later. Extremely rapid accumulation of fluid in the pleural cavity is a characteristic sign of carcinoma of the pleura. Pleurisy sometimes develops insidiously with no sharp deterioration in the patient's condition, high leucocytosis or chills.

Microfocal pneumonia is an acute disease occurring in full health. It is marked by toxicosis and signs which disappear without a trace a short while after medication with antibiotics. Gentomycin or kanamycin in combination with carbenicillin are the preparations of choice in trial therapy of such cases. Some clinicians prefer first to give less toxic antibiotics, e.g. ceporine alone or together with carbenicillin (Seneca and Grant, 1976). If pneumonia is complicated by pleurisy with effusion (usually purulent), the patient's condition

grows sharply worse, toxicosis intensifies, high leucocytosis develops, and high fever with chills and sweating appears.

The search for metastases to the subcutaneous lymph nodes sometimes proves successful. Biopsy of such a node may not only help in making the diagnosis but also in searching for the primary tumour. Special methods of examination of all internal organs and consultations with specialists are resorted to in order to reveal the source of metastasis.

Sarcoidosis. According to Rabukhin et al. (1975), 9.4 per cent of all patients with sarcoidosis are sent to the clinic with the diagnosis of 'pneumonia'. It is usually made in stage II sarcoidosis when the pathological process spreads to the lungs. The lymph nodes in the pulmonary roots often diminish noticeably in size by this time. In approximately 25 per cent of patients they disappear completely.

The spread of the process to the lungs is often attended by fever. Cough, rales in the lungs, arthralgia and pain in the muscles appear. Chest pain is explained by frequent and usually severe cough but not by involvement of the pleura in the process, since serous membranes are almost never involved in sarcoidosis. The complex of clinical symptoms described makes it necessary to resort to X-ray examination which demonstrates miliary or microfocal shadows scattered diffusely in one or both lungs. In some cases, these shadows are seen separately, in others they coalesce, forming large nonhomogeneous densities resembling those in bacterial pneumonias. Focal shadows in sarcoidosis, like those in pneumonia, differ in size and shape; they are mostly localized in the middle and lower pulmonary lobes.

Sarcoidosis differs from pneumonia in the clinical form and in involvement of other organs and systems in the pathological process. Affection of the peripheral lymph nodes is a particularly frequent finding (73-100 per cent of cases). Lesions of the skin, joints and eyes and hepatomegaly and splenomegaly are found in about one third of cases. Blood changes in sarcoidosis noticeably differ from those in pneumonias. It is relatively easy to make the differential diagnosis between microfocal pneumonias and the pulmonary form of sarcoidosis. It is far more difficult to distinguish sarcoidosis from miliary carcinosis and particularly from haematogenous disseminated pulmonary tuberculosis.

A combination of fever with microfocal affection of the lungs is encountered in rare cases of **tertiary syphilis of the lungs.** Gummas may form in both lungs, mainly in the middle and lower parts. They are clearly outlined and never calcified or coalesced. It is difficult to distinguish them from microfocal pneumonia and haematogenous disseminated pulmonary tuberculosis. The diagnosis of syphilis of the lungs is verified by positive Wasserman's and

Treponema pallidum immobilization tests and good results of penicillin therapy.

The dissemination of lymphogranulomatosis from the lymph nodes of the mediastinum or other regions sometimes leads to the formation of miliary focal shadows in the lungs which, in combination with fever, may be mistaken for lobular pneumonia, miliary tuberculosis of the lungs, sarcoidosis or carcinosis. Either one (lymphogenic miliarization) or both lungs (haematogenic miliarization) are involved. Miliary and submiliary forms of lymphogranulomatosis always develop as a secondary condition and are therefore easily distinguished from diffuse microfocal bacterial and virus pneumonias. It is more difficult to make the differential diagnosis between the miliary form of lymphogranulomatosis, miliary tuberculosis of the lungs or sarcoidosis.

Occupational diseases of the lungs. Microfocal shadows are often found in many occupational diseases. They develop with particular constancy in exposure to mineral dusts (among which fragments of silica, talcum and asbestos are most aggressive) and organic substances (among which fragments of cotton, flax, hemp are considered most aggressive; it has recently been established that mouldy hay and straw, together with the fungi in them, should also be included in this group). Fever and the formation of small foci of pneumonia are always encountered following exposure to many gaseous substances widely spread in industry and farming.

That is why, in taking the medical history, it is essential to question the patient in detail not only about the manifestations and course of the given disease and about past diseases, but also about his past and present occupations. It is important to clarify the character of the production in which he was employed and how long he worked there. The true cause of the disease in many such cases may be identified only after consultation with a specialist in occupational pathology. For instance, granulomatous inflammation of the lungs with marked fibrous sclerotic changes in a patient who had handled beryllium at his job ten years previously, may prove to be not sarcoidosis, but chronic berylliosis. It was initially believed that contact with organic dust may lead to the development in some patients of acute allergic pneumonia described above. It has now been proved that subacute and chronic forms of these pneumonias exist. They are marked by fever, chills, cough with bloodstained sputum, and the formation of small foci of pneumonia with diffuse involvement of both lungs. The clinical and X-ray signs of this pneumonia may disappear only after contact of the patient with substances causing this pneumonia is discontinued (e.g. flax, hemp, oats, hay or other substances). A consultation with a specialist in occupational pathology may prove invaluable in identifying the cause of pneumonia in such cases.

Diffuse fibroplastic alveolitis. The subacute form of this disease was described for the first time in 1944 by Hamman and Rich. It has now been established that the chronic form of diffuse fibroplastic alveolitis is encountered much more frequently than the subacute form. The disease begins with the accumulation of large mononuclear cells in the alveoli. The walls of the alveoli become thicker and infiltrated with plasma cells, lymphocytes, giant cells and eosinophils.

The first clinical manifestations of the disease are fever and cough in attendance to which dyspnoea soon develops. Crepitation is heard over both lungs and is particularly intensive over the basal segments of the lower lobes. Dry and moist rales appear if secondary infection develops. X-ray examination demonstrates bilateral focal shadows which are larger and more numerous in the lower lobes. In subacute cases the focal shadows in the lower lobes often coalesce.

The combination of focal shadows with fever and rales in the lungs gives grounds for diagnosing pneumonia at first. Under the effect of chemotherapy body temperature may fall to normal but the changes in the lungs and dyspnoea increase. Cyanosis soon also develops. Dyspnoea and cyanosis progress gradually and it becomes obvious that it is not simple pneumonia that the patient is suffering from. Despite the growing infiltration of the lungs, the patient never experiences pain in the chest. Sometimes changes are seen in the end phalanges of the fingers which become clubbed. The final diagnosis is established from the combination of the above described clinical picture of the disease with the typical changes in the lungs. To reveal these changes biopsy is necessary.

Prehilar Pneumonia

Pneumonias localized in the region of the pulmonary root possess a number of specific clinical features. In many cases of these pneumonias, there is no chest pain even in the acute period of the disease. The inflammatory process sometimes extends to the paramediastinal space and X-ray examination demonstrates a shadow in which even the heart boundaries are distinguished with difficulty. The results of percussion and auscultation sometimes yield incorrect information on the location of the inflammatory process. Bronchial respiration and rales are often heard over the healthy lung in prehilar pneumonias. The true location of pneumonia in such cases can be determined by auscultating the patient as he lies on the involved side, or by X-ray examination.

The localization of pneumonia creates additional difficulties in interpreting the results of X-ray examination. The shadow produced by the focus of prehilar pneumonia merges with the pulmonary

root and the resulting X-ray picture is distinguished with difficulty from distension of the pulmonary root in primary tuberculosis, tumours, and some other diseases listed in Supplement XXII-1. Most frequently prehilar pneumonia must be differentiated from pulmonary tuberculosis and bronchial carcinoma. These three diseases are marked by increased body temperature, cough, leucocytosis and increased ESR. In most cases, prehilar pneumonia resolves completely two to four weeks from the onset of the disease. Sometimes it takes a protracted course, which creates additional difficulties for distinguishing it from the diseases discussed above.

Tuberculosis of the lungs. Two forms of tuberculous bronchadenitis are commonly distinguished, inflammatory and tumour-like. The first form usually begins abruptly, but the process soon develops into the phase of resolution and thickening. The course of the tumour-like form is more torpid. The root of the lung usually acquires nodular polycyclic contours. Pressure exerted on the adjoining organs may lead to the development of lobar and segmental atelectasis of the lung and to compression of vena cava superior. These complications are very rare in adults. The process usually causes no marked disorders in their general condition. Subfebrile body temperature and a cough with a small amount of sputum are encountered.

Severe toxicosis develops in the acute period of bacterial prehilar pneumonia, but the general condition of a patient with virus pneumonia is satisfactory from the onset. A tormenting cough is a characteristic sign of tuberculous bronchadenitis and of virus pneumonia. In protracted pneumonia, the patient's condition is usually satisfactory. Body temperature is usually subfebrile. Although these diseases closely resemble each other in their clinical picture, they nonetheless can be distinguished if attention is focused on the evolution of the symptoms and signs of the disease under the effect of treatment and the degree of the phenomena of tuberculous allergization.

The results of tuberculin tests may be of immense assistance in the differential diagnosis of pneumonia. Adults with negative tuberculin tests are often encountered today and it is therefore extremely important to ask the patient about previously suffered influenza-like diseases and pneumonias, about his tendency to have repeated influenza-like diseases and their duration; the time of the appearance of positive tuberculin reactions is determined and the character of tuberculin tests during the present disease revealed. Tuberculin tests acquire particular differential diagnostic significance if Pirquet's reaction becomes positive during the given disease. Tuberculous bronchadenitis is a component of the primary complex and the attendant exacerbation of fever often occurs after

a long period of subfebrile temperature. Prehilar pneumonia, on the contrary, is an acute disease. The patient had been in full health before it developed. Bacterioscopic and bacteriologic examination of the sputum in tuberculosis may reveal the decisive diagnostic sign, i.e. *M. tuberculosis*. Treatment with antibiotics and sulphanilamides may considerably improve the condition of a patient with prehilar pneumonia, but produces no effect on the course of the tuberculous process. The involution of an infiltrative pulmonary root under the effect of treatment with tuberculostatic agents is extremely slow and is beyond comparison with the rate of involution of bacterial or virus pneumonia. Dense focal shadows always remain in the lungs after tuberculous infiltrated resolve, while petrificates form later. Infiltration of the lungs in prehilar pneumonia usually leaves no traces.

The record of typical complications may also considerably help in the differential diagnosis of these diseases. Involvement of the lymph nodes in other body regions and pleurisy with effusion are characteristic of primary tuberculosis. The formation of abscesses is the most typical complication in prehilar pneumonia. This is manifested by recurrent chills, sharp deterioration in the general condition, high leucocytosis and often by expectoration of fetid sputum. Pleurisy with effusion (usually purulent) is also among the severe complications of pneumonia and its development is attended by severe pleural pain and a new wave of high fever and high leucocytosis. These two diseases differ not as much in their symptoms as in the degree of manifestations of these symptoms and the character of their evolution under the effect of therapeutic measures and in the course of the disease.

Tumour of the bronchus. Prehilar pneumonia must at times be distinguished from central carcinoma of the lungs. Both diseases may be attended by long-term fever, leucocytosis, cough and may be complicated by pulmonary abscess. In both diseases X-ray reveals enlargement of one of the pulmonary roots with more or less marked prehilar infiltration. Personal bitter experience has shown that very serious difficulties arise at times when the differential diagnosis between these diseases is considered. This is rather explained by the fact that it is far from every case of central pulmonary carcinoma that atelectasis of the lobe or segment develops.

The prehilar shadow in central carcinoma is often irregular in shape. It gradually diminishes in the direction of the periphery and is continuous with the pulmonary tissue without any clearly defined boundaries. With the growth of the tumour its shadow on the radiograph becomes heterogeneous. Hypoventilation of the corresponding segment develops in later stages. Infection of this segment leads to pneumonia which is often complicated by pulmonary tissue disintegration. Our experience shows that prehilar pneumonia in

middle-aged and elderly patients often proves to be complicated bronchial carcinoma.

Information concerning the state of health before the onset of the disease may help greatly in the differential diagnosis between prehilar pneumonia and central pulmonary carcinoma complicated by pneumonia. Pneumonia is a late complication of bronchial carcinoma. It is preceded by a rather lengthy period of cough, chest pain and sometimes haemoptysis and fever. Bacterial and virus pneumonias of prehilar localization arise in full health or after a few days of indisposition associated with a respiratory infection. There is no doubt that the results of special methods of examination are more reliable differential diagnostic criteria.

Prehilar pulmonary carcinoma is localized in the main, lobar, and less frequently, in the segmental bronchi, i.e. in places accessible to bronchoscopy. Moreover, the condition of the lobar bronchi and bronchopulmonary lymph nodes can be studied by tomography. The structures of the prehilar shadows and the condition of the lumen of the large bronchi are also clearly visible. Carcinoma of a bronchus may be spoken of in those cases in which tomograms demonstrate a stump or constriction of one of the large bronchi and a heterogeneous shadow of the tumour itself from which protrusions in the form of bundles stretch to the periphery of the lung.

Clinical and X-ray signs of atelectases of a lobe or segment (diminished volume of the lobe, displacement of the mediastinum to the involved side, elevation of the diaphragm on the involved side) are encountered only in the late stages of the disease, usually simultaneously with the development of pleurisy with effusion.

Lymphogranulomatosis. Most patients suffering from lymphogranulomatosis apply for medical advice because of enlargement of the lymph nodes. Enlargement of the mediastinal lymph nodes, isolated or in combination with enlargement of the nodes of the pulmonary roots, is the first to be encountered. Most clinicians claim that the right lung is involved more frequently than the left. Kaplan (1972) reports that fever found during the patient's first visit to the doctor is often caused not by lymphogranulomatosis itself, but by intercurrent diseases (influenza, bronchitis, pneumonia). After a course of antibiotic therapy the patient's condition improves noticeably, but subfebrile temperature or moderate fever continues.

X-ray examination conducted at the onset of the disease or in the period of 'postinfection' subfebrile temperature sometimes demonstrates a prehilar density which gradually diminishes in intensity and becomes continuous with the pulmonary tissue. The infiltration around the pulmonary root is sometimes so intensive that the lymph nodes from which the tumorous tissue had arisen cannot be seen. Radiographs show a rather coarse reticular pattern and many

small focal shadows of an irregular shape. According to Strickland (1967), involvement of the pulmonary parenchyma may be the only sign of lymphogranulomatosis in very rare cases. The mediastinal lymph nodes are normal in such instances.

The true cause of prehilar pulmonary infiltration in such cases may be identified only when a longer follow-up reveals other intra- or extrathoracic signs of lymphogranulomatosis.

Supplement XXII-1

Pneumonia

I. Acute pneumonia.
  1. Bacterial (Gram-positive).
    Pneumococcal.
    Staphylococcal.
    Streptococcal.
    Anaerobic.
    Other Gram-positive pneumonias.
  2. Bacterial (Gram-negative).
    Haemophilus influenzae pneumonia.
    Klebsiella pneumonia.
    Enterobacterial pneumonia.
    Serratia pneumonia.
    Coli pneumonia.
    Pyocyaneus pneumonia.
    Proteus pneumonia.
    Acinetobacterial pneumonia.
    Legionellosis (legionnaires' disease).
    Other Gram-negative pneumonias.
  3. Virus and mycoplasmal pneumonias.
    Mycoplasmal.
    Adenovirus.
    Influenzal.
    Other virus pneumonias.
  4. Chlamydial and rickettsial pneumonia.
    Ornithosis.
    Pneumonia in Q fever.
  5. Allergic pneumonias.
    Pneumonias caused by organic dust aspiration.
    Loeffler's syndrome.
  6. Pneumonias caused by the effect of physical factors, aspiration or inhalation of aerosoles, gases, and other substances.
    Lipoid.
    Hydrocarbon.
    Radiation.
    Other pneumonias.

II. Unresolved pneumonia.
  1. Lobar and segmental unresolved pneumonia.
    Infiltrative pneumonic pulmonary tuberculosis.
    Bronchogenic pulmonary carcinoma.
    Alveolar carcinoma of the lung.
    Bronchial adenoma.

Lymphogranulomatosis of the lung.

2. Lobular unresolved pneumonia.
   Pulmonary infarction.
   Alveolar carcinoma of the lung.
   Pulmonary tuberculosis.
   Solitary metastases of a tumour to the lung.
   Adenoma arising from a peripheral bronchus.
   Tuberculoma (caseoma) of the lung.
   Lymphogranulomatosis of the lung.
   Lymphosarcoma of the lung.
3. Diffuse miliary pneumonia.
   Tuberculosis of the lung.
   Miliary carcinosis.
   Sarcoidosis.
   Pulmonary syphilis.
   Lymphogranulomatosis.
   Occupational diseases of the lung.
   Diffuse fibroplastic alveolitis.
4. Prehilar unresolved pneumonia.
   Tuberculosis of the lungs.
   Tumour of a bronchus.
   Lymphogranulomatosis.

Chapter XXIII

Polycythaemia

Just as other authors we use the term 'polycythaemia' not literally, but for designating a group of diseases manifested by an increased volume of packed red blood cells in the body, i.e. their increased volume per 1 kg of body mass. Clinically, this is displayed by an absolute increase in the number of red cells which is often, although not always, attended by an increase in haemoglobin concentration and the share of red cells in the total blood volume.

On the average, the red cell volume is 36 ml/kg in the body of a healthy male, and 32 ml/kg in the body of a female. Oxygen saturation of arterial blood in a healthy person does not fall below 92 per cent. Absolute polycythaemia (an independent disease of unknown aetiology which is marked by proliferation of all bone-marrow germs) and secondary or symptomatic, polycythaemia (manifested by an increased total red cell mass in the body without concomitant involvement of other bone-marrow germs in the process) are distinguished. Moreover, relative or false polycythaemia is also distinguished in which the mass of red cells in the body does not change but the concentration of red cells and haemoglobin in the blood is elevated because of a decrease in the plasma volume. Thus, relative polycythaemia can easily be differentiated from polycythaemia vera and symptomatic polycythaemia by determining the red cell volume per 1 kg of body mass.

The clinical picture of **polycythaemia vera** was first described by Vaquez in 1892. The disease is usually discovered in middle age. Its incidence among males is about twice that among females. Polycythaemia is hardly encountered in children. In clearly manifested cases polycythaemia is easily diagnosed by the entirety of the following signs: reddish cyanosis (plum colour) of the face and limbs, skin ecchimoses, sharply marked network of dilated blood vessels of the eye conjunctiva and sclera, engorgement of visible mucous membranes, marked splenomegaly, hyperplastic bone marrow, increased red-cell, leucocyte and blood-platelet count, increased haemoglobin concentration in blood and increased haematocrit value. Most of these symptoms and signs are explained by an increase in the total blood volume, increased blood viscosity and diminished rate of blood flow in the vessels overfilled with red cells, in the capillaries and veins in particular.

In most cases, the disease begins insidiously with diminished tolerance of the habitual working and everyday loads. Dyspnoea, dizziness, headache and visual disorders develop in attendance later. Some patients experience itching in the whole body which

is characteristically intensified after a hot bath. Some patients complain of burning or throbbing pain in the feet, legs and hands. The skin on the hands and feet is dark red. Raynaud's syndrome sometimes develops.

Patients with polycythaemia have a characteristic paradoxical tendency to simultaneous occurrence of thromboses and increased tendency to bleeding. Purpura is among the characteristic signs of this disease. Approximately 10 to 19 per cent of patients have gastric or duodenal ulcer which may be complicated by profuse gastrointestinal bleeding. Females suffering from polycythaemia often have uterine haemorrhages which are sometimes so profuse that iron deficiency anaemia develops. Minor wounds, for instance, after tooth extraction, are often complicated by massive bleeding.

Simultaneously with the tendency to bleeding, patients with polycythaemia easily succumb to intravascular thromboses. Thromboses of the small vessels of the hands and feet are encountered particularly frequently and are sometimes misdiagnosed as thrombophlebitis. Thromboses of larger arteries and veins occur with particular constancy in the heart, brain, liver, spleen and the lungs. Thrombosis of the coronary or cerebral artery is sometimes the first disorder compelling the patient or his relatives to apply to a physician who is the one to discover the true cause of the stroke, myocardial infarction or acute thrombosis of the portal vein.

Changes in the size of the spleen in polycythaemia are of considerable diagnostic and of no less prognostic significance. Splenomegaly is revealed in about 75 per cent of patients by the time the diagnosis is established. Its rounded firm edge is usually felt 1 or 2 cm below the costal arch. With time, the spleen becomes enlarged. The larger the spleen, the more probable the development of foci of myeloid metaplasia in it; the longer the disease lasts the more frequently is hepatomegaly found. Moderate or marked elevation of arterial pressure with concomitant left-ventricular hypertrophy is revealed in about half of the patients with a marked picture of the disease.

The results of laboratory tests are of high diagnostic significance. Erythrocytosis is the most typical sign of the disease. The number of red cells in 1 ml of blood increases to 7 to 10 mln, while the haemoglobin content grows to 180 to 240 g/l. Depending on the severity of the disease, the haematocrit value ranges from 55/45 to 70/30. As it is noted above, the red cell mass increases sharply in polycythaemia, whereas the plasma volume may be normal, slightly increased or even reduced. The content of haemoglobin and red cells in the blood may fall sharply in a patient who had recently suffered from a haemorrhage. Even short-term iron deficiency anaemia sometimes develops after a massive haemorrhage.

Polycythaemia is usually attended by moderate leucocytosis and

thrombocytosis. In 50 to 70 per cent of patients with no signs of any infection, the blood leucocyte count is usually increased to $10 \cdot 10^3$-$12 \cdot 10^3$ per 1 μl. In rare cases, leucocytosis is still higher. The increased number of leucocytes is explained by their faster production in the bone marrow. The regular increase in the blood platelet count explains the specific tendency of polycythaemia patients to develop vascular thrombi.

Signs of hyperplasia usually of the erythrocytic and megakaryocytic germs are detected in bone marrow aspirates. Just as in other myeloproliferative syndromes, increased concentration of alkaline phosphatase, uric acid and vitamin B_{12} is often found in the serum of patients with polycythaemia.

Before the introduction of the modern therapeutic methods, the life survival of a polycythaemia patient ranged from 1 to 25 years from the moment the diagnosis was established, and was 6.7 years, on the average. With the modern methods of treatment, the average survival period doubled. The chronic slow progressive course of polycythaemia is interrupted from time to time by acute complications caused either by thromboses or by haemorrhages. Thrombosis may occur in any vessel, but is most commonly encountered in the branches of the portal vein and in the cerebral and coronary arteries; such thromboses are complicated by strokes, myocardial infarction and portal hypertension.

The diagnosis of polycythaemia vera proves to be simple in many cases. The disease is suspected because of the patient's appearance. The suspicion becomes grounded after tests for the red cell mass. The diagnosis is considered verified if no disease capable of being complicated by symptomatic (secondary) polycythaemia is found. It is our experience that polycythaemia vera remains unrecognized for a lengthy period of time. Most frequently we had to differentiate it from hypertensive disease, cirrhosis of the liver, leukaemia and renal colic.

In the early stages of development, polycythaemia is often mistaken for *hypertensive disease*. The red cell mass is slightly increased in this period of the disease and there are still no characteristic signs of engorgement of the vessels of the skin, eyes and mucous membranes. Complaints of weakening memory, headache, dizziness, tinnitus, dyspnoea and pain in the region of the heart in middle-aged patients suggest, before all else, that this is a case of the most commonly encountered atherosclerosis of the coronary and cerebral arteries. The increased arterial pressure fully explains the headache, tinnitus and possibly, the rather early appearance of angina pectoris. Intermittent claudication typical of polycythaemia is taken for still another manifestation of systemic atherosclerosis, of the lower limbs in the given case. The occurrence of myocardial infarction or stroke in polycythaemia is sometimes taken for a regular

complication of ischaemic disease of the heart or brain, while the attendant heart failure is considered to be a consequence of cardiosclerosis.

The failure of hypotensive therapy in a patient suffering from increased arterial pressure is often the first factor to prompt the physician to reconsider some of the links in the chain of logical reasoning presented above. In most cases of non-malignant hypertensive disease following an ordinary course, the combined effect of bedrest and modern hypotensive agents normalizes arterial pressure and causes the disappearance of the subjective manifestations of the disease. The same therapy may normalize arterial pressure in cases of polycythaemia, but does not change the subjective picture of the disease. As formerly, the patients complain of attacks of angina pectoris, tinnitus and headache.

The number of diagnostic errors would have been much less if the clinical picture of the disease were compared without fail with the condition of the fundus oculi in every case of arterial hypertension. In polycythaemia with increased arterial pressure, the vessels of the fundus are always engorged and the flow of blood in them is always decelerated. Such a picture of the fundus is never encountered in hypertensive disease, which is characterized by spasm of the arteries and normal or diminished blood filling of the capillaries.

An increased number of leucocytes and blood platelets in the blood is a typical sign of polycythaemia. Hypertensive disease is attended by leucocytosis only if complicated by infection. Increased blood platelet count, purpura and an extraordinary tendency of the minor wounds to bleed are characteristic of polycythaemia but are not encountered in hypertensive disease.

The combination of increased arterial pressure and splenomegaly is a cardinal sign of polycythaemia. Whenever this sign is present, polycythaemia must be suspected and the total red cell mass determined. This is most accurately determined by means of radioactive chromium. The diagnosis of polycythaemia may be considered firmly established if the patient has an enlarged spleen and the red cell mass exceeds the normal values listed above.

Attacks of acute pain in the left hypochondrium which are usually induced by splenic infarction often occur in far-advanced cases of polycythaemia with increased arterial pressure, dyspnoea, headache, angina pectoris and a characteristic appearance of the patient. Sometimes this pain is mistaken for *left renal colic*. The true cause of the malady may usually be determined at the patient's bedside without resorting to additional examination. The pain in infarction of the spleen is either localized or referred upward to the left arm, whereas pain in left renal colic is referred downward to the left inguinal region and the left testis. Pain in infarction of the spleen

intensifies during respiration and when pressure is exerted on the left hypochondrium. Pain in renal colic does not depend on respiration. The peritoneal rub is sometimes heard over the spleen involved in infarction, but is never heard in renal colic or in renal infarction. A characteristic urinary syndrome naturally appears both in renal colic and in infarction of the kidneys. Urinalysis in infarction of the spleen shows normal values. Decisive significance should nevertheless be attached to identification of the signs of the principal disease.

Marked increase of blood viscosity in far-advanced polycythaemia cases is complicated by thromboses of small and larger vessels. Thrombi form with particular regularity in vessels in which blood flows very slowly. This explains the especially frequent thromboses in the splenic branches of the portal vein. The developing portal hypertension intensifies blood stasis in the bed of the portal vein and facilitates the development of portacaval anastomoses and ascites. The clinical picture of the disease in such cases resembles the picture of *cirrhosis of the liver.*

The cause of ascites and the hepatolienal syndrome may be identified correctly in most cases of this kind at the patient's bedside.

Polycythaemia with ascites, hepatomegaly and splenomegaly differs from true cirrhosis of the liver in the marked character of the attendant signs of the disease. Arterial pressure is often increased in polycythaemia patients. In all cases in our practice the number of red cells and platelets in blood was normal or increased and the patients complained of headache, dizziness, tinnitus, attacks of angina pectoris, intermittent claudication and dyspnoea. Signs of previous myocardial infarction are often demonstrated on the ECG of these patients. The content of vitamin B_{12} and alkaline phosphatase in the blood increases.

The ascitic stage of cirrhosis of the liver is marked by emaciation of the patient, the arterial pressure is normal or reduced, the blood plasma protein content is also reduced and anaemia is often found. The muscles of the upper trunk are atrophied and spider naevi are often seen on the skin.

The final diagnosis may be verified by the results of needle biopsy of the liver. The structure of the liver in polycythaemia is normal. The findings of needle biopsy in cirrhosis provide evidence of disorders in the normal architecture of the hepatic lobules and signs of inflammation in the connective tissue surrounding them. These diseases also differ in the results of scintigraphy of the liver and portography but there is usually no need to resort to these studies.

Immature cells of the myeloid series appear in peripheral blood 10 to 20 years after the onset of polycythaemia. They differ from immature cells occurring in chronic myeloid leukaemia in the con-

tent of alkaline phosphatase, glycogen and histamine. In such cases it is usually said that polycythaemia has transformed to myeloid leukaemia or myeloid fibrosis. Manifest cases of polycythaemia differ sharply from myeloid leukaemia, but this is not true of their initial manifestations when both diseases may be marked by moderate splenomegaly, hyperplasia of all bone marrow germs, and a slight increase in the red cell mass.

The difficulties in the differential diagnosis in such cases may sometimes be overcome by correlating the onset of the disease with the patient's age. Polycythaemia sets in at middle age, as a rule, whereas leukaemias are often encountered in the young. This rule is not absolute and cannot be applied in the analysis of an individual case.

The final diagnosis can usually be established only after the course of the disease is followed for some period. With time a patient with polycythaemia acquires a characteristic appearance caused by an abnormally high number of red cells; the number of blood platelets and the haematocrit values grow and angina pectoris develops. The advancement of myeloid leukaemia is attended by loss of body weight, fever (usually moderate), sweating at night, and anaemia which is always of haemolytic origin. The differential diagnosis is made in most cases without resorting to sternal puncture.

The number of red cells in the blood may increase for a long time under the effect of many factors; a particularly significant role is played by some hormones, the blood oxygen content, the structural peculiarities of the haemoglobin molecule, etc. The forms of secondary polycythaemia arising in these disorders may be divided into three groups according to the factors which had induced them. The smallest of these groups is the recently described *congenital polycythaemia*, or primary erithrocytosis, whereas the most widespread is the group of *secondary polycythaemias* associated with tissue hypoxia. We set polycythaemias occurring at times in cases of tumours in a separate group, because the mechanisms of their development are not clear.

Congenital Polycythaemia

Congenital polycythaemia has been studied mainly in children. Autosomal dominant and recessive forms of the disease have been described. The mechanisms of development of polycythaemia are still insufficiently clear. The disease is manifested as a selective increase in the number of red cells. The number of leucocytes and platelets in the blood does not change. The spleen is modera-

tely enlarged. The disease begins in childhood and follows a b nign course usually with moderate splenomegaly. Thromboemboli complications are nonetheless encountered somewhat more fr quently in patients with congenital polycythaemia than in health persons.

Hypoxic Polycythaemia

Secondary polycythaemia always develops in tissue hypoxi which the clinician encounters most frequently in diseases of th lungs and the cardiovascular system and among inhabitants c high-altitude areas. It has been recently disclosed that some of th chronic polycythaemias are associated with the existence in th blood of previously unknown anomalous haemoglobins.

Polycythaemia due to oxygen deficiency in the arterial bloo always develops in *pulmonary stenosis*, *chronic heart failure* an in all *developmental anomalies of the heart and vessels* marked b shunting of blood from the veins into the arteries. In applicatio to pulmonary circulation, these will be usually congenital arteric venous anastomoses with shunting of the blood from the artery t the pulmonary veins. Cyanosis in these patients is attended by clubb ing of the end phalanges of the fingers and toes. Increase in th number of red cells is attended neither by leucocytosis nor by throm bocytosis. The spleen is normal in size.

Polycythaemia is often encountered in chronic bronchitis, sarcoid osis, pneumosclerosis, obstructive pulmonary emphysema, silicosi and many other pulmonary diseases marked by a reduced oxyge content in the blood. It is a constant sign of Pickwick's syndrom developing in extreme degrees of obesity. It is also often observe in diseases of the nervous system marked by alveolar hypoventila tion, e.g. in poliomyelitis, amyotrophic lateral sclerosis, and myas thenic states.

Lack of oxygen in the inspired air is the cause of *polycythaemi in inhabitants of high-altitude regions*. Polycythaemia may develo as early as seven or eight days of living at an altitude of abou 3000 metres above sea level. Its development is attended neithe by splenomegaly, leucocytosis, nor by thrombocytosis. Soo after the mountaineer descends to sea level, this polycythaemi vanishes.

Some drugs (acetophenetidin, acetanilide, sulphamides, etc.) ma noticeably reduce the blood oxygen content and even lead to cyanosi caused by the accumulation of methaemoglobin and sulph-haemc globin in the blood. Cyanosis disappears when these drugs are dis continued. Besides the forms of acquired and short-term hypoxaemi mentioned above, there are congenital haemoglobin anomalies whic

lead to the development not only of hypoxaemia, but of polycythaemia.

Congenital deficiency of enzymes of the reductase group causes the accumulation of methaemoglobin in the red cells. These *congenital methaemoglobinaemias* are marked by cyanosis and polycythaemia which develop soon after birth. The second form of congenital methaemoglobinaemia is explained by inheritance of a variant of haemoglobin known as haemoglobin M. It is inherited as a dominant trait. This haemoglobin anomaly is manifested clinically by cyanosis, which is usually mild. Haemoglobin M may be differentiated from the other forms of methaemoglobin by electrophoresis and spectrophotometry.

In the last ten years there have been evermore frequent reports on cases of polycythaemia in which haemoglobinopathy may be revealed only by a characteristic shift to the left of the oxygen dissociation curve. This group of haemoglobinopathies is also inherited. They are not demonstrated by electrophoresis.

The significance of these discoveries consists in the fact that they have shown the necessity for a stricter approach to the diagnosis of polycythaemia vera. Polycythaemia of unclear origin may be diagnosed as polycythaemia vera only when its possible association with these newly discovered forms of haemoglobinopathies is ruled out.

The development of polycythaemia in the diseases listed above is attributed to increased production of erythropoietin which forms under the effect of hypoxia and stimulates the bone marrow. Secondary polycythaemia in some forms of Itsenko-Cushing's syndrome is also explained by the effect of androgens and corticosteroids on bone marrow function. Increased production of erythropoietin is most likely one of the intermediate links of their effect on haematopoiesis.

Hypoxaemia is a frequent though not an obligatory cause of polycythaemia. Changes in the number of red blood cells in cases of *different tumours* are evidence of this. Secondary polycythaemia develops particularly frequently in diseases of the kidneys, namely, hydronephrosis, solitary and multiple cysts, hypernephroma and polycystic disease. Secondary polycythaemia is often encountered in tumours of other organs. It has been described in tumours of the ovary, fibromyoma of the uterus, pheochromocytoma, primary carcinoma of the liver and tumours of the posterior cranial fossa. These polycythaemias disappear soon after successful surgery.

Many other tumours, for instance, carcinoma of the lung, carcinoma of the stomach with metastases in the liver, and multiple myeloma are also attended sometimes by an increased number of red cells, leucocytes and blood platelets. The cause of polycythaemia in such cases is not known.

Relative Polycythaemia

Short- or long-term increase in the plasma volume causes an increase in the number of formed elements in the blood in a unit of its volume, i.e. it leads to polycythaemia which is generally called 'relative polycythaemia' or 'pseudopolycythaemia'. This syndrome develops in severe vomiting, for instance, vomiting in pregnancy, in diabetes mellitus or diabetes insipidus, and in protracted shock. The developmental mechanisms of this syndrome may differ in some cases. Relative polycythaemia takes a benign course, i.e. without a marked tendency to thromboses and the development of a stable increased viscosity syndrome. The diagnosis of relative polycythaemia is made in those cases when the plasma volume is less than 35 to 45 ml/kg.

Supplement XXIII-1

Causes and Types of Polycythaemia

1. Absolute polycythaemia.
2. Secondary (symptomatic) polycythaemia.
   - Congenital polycythaemia.
     - Primary erythrocytosis.
     - Hereditary haemoglobinopathy.
       - Reductase deficiency.
       - Increase in haemoglobin M.
       - Oxygen dissociation disorders.
   - Acquired polycythaemia.
     - Mountain sickness.
     - Diseases of the cardiovascular system.
       - Congenital diseases of the heart and vessels complicated by cyanosis.
       - Chronic heart failure.
     - Diseases of the lungs with disturbed oxygen diffusion.
     - Diseases of the nervous system marked by disorders of pulmonary ventilation.
     - Obesity.
   - Malignant tumours.
   - Drugs.
3. Relative polycythaemia.
   - Reduced blood plasma volume.

Chapter XXIV

Polyuria and Polydipsia

The volume of urine is mainly determined by the osmotic load experienced by the kidney. A healthy person usually excretes 1.0 to 1.5 litres of urine daily. In rare cases, the daily diuresis reaches 2.5 litres. The term 'polyuria' designates conditions characterized by the constant excretion of more than 2.5 litres of urine daily.

In polyuria, urine is excreted more frequently than ordinarily both during day and night. Polyuria must be differentiated from pollakiuria in which urine is excreted more frequently than normally, but in small portions, and from nycturia with a characteristic distortion of the daily micturition rate. Most of the daily amount of urine is excreted at night in nycturia, but the total volume is normal or even reduced. Pollakiuria is mostly encountered in pyelocystitis, whereas nycturia occurs in heart failure, the nephrotic syndrome, and chronic renal failure.

Any increased osmotic load on the kidney is attended by polyuria. Temporary polyuria is a consequence of the prescription of drugs in most cases. This chapter deals with permanent polyuria the osmotic and water forms of which are generally distinguished. Although it is necessary to know the mechanisms of the clinical syndromes, it is even more important to know the causes of their development. Unfortunately, we have as yet not studied the mechanisms of polyuria deeply enough and despite all efforts we have failed to clarify their causes. The clinical synthesis of both principles is shown in Supplement XXIV-1 which we employ in the analysis of polyuria.

It is expedient to distinguish four causes of polyuria: osmotic diuresis; the patient's incapacity for secreting an adequate amount of the antidiuretic hormone; diminished concentrating power of the kidneys despite the normal content of the antidiuretic hormone in blood; involuntary polydipsia. In most cases of polyuria due to incapacity of the kidney to concentrate the urine when the blood antidiuretic hormone content is normal, the daily diuresis almost never exceeds three or four litres. Osmotic diuresis rarely exceeds five or six litres daily. The daily urine volume in involuntary polydipsia and pituitary diabetes (diabetes insipidus) ranges from 4 to 15 litres. In some cases it may even be more.

Diabetes Mellitus

The clinical picture of diabetes was first described by Celsus (1st century A.D.), the famous philosopher and physician. A line of distinction between diabetes with 'tasteless' urine (diabetes insipidus) and diabetes in which the patient's urine was 'sweet as honey' (diabetes mellitus) was drawn in the 17th century.

The onset of diabetes mellitus may be abrupt or insidious. An abrupt onset is usually encountered in children. Polyuria is often the first sign which attracts the parents' attention. It is usually manifested as nocturnal enuresis. Having learnt to awaken at night to evacuate his bladder the child again becomes messy. Quite often coma is the first sign of the disease after which the anxious parents pay closer attention to the child and find that he has polyuria and polydipsia.

Polyuria is often the first sign of diabetes mellitus in adults. At the same time dryness in the mouth and abnormal thirst appear. Other signs of severe diabetes develop quite soon: polyphagia, periodontosis, skin itch and progressive weakness. Most untreated individuals lose body weight rapidly, sometimes as much as 15 to 20 kg within a month.

The diagnosis of severe diabetes mellitus with absolute insulin deficiency is relatively easy. The vividly manifested two paired signs, namely, polydipsia with polyuria and polyphagia with loss of body weight, suggest diabetes. The final diagnosis is based on the discovery of reduced level of free insulin in the blood, hyperglycaemia and glucosuria.

In appraising the results of laboratory tests, it should be borne in mind that the test for the concentration of immunoreactive insulin in blood yields the most reliable results and that positive Fehling's and Benedict's tests indicate the presence in the urine not only of glucose, but of many other reducing substances. False positive results may be due to the presence of other sugars in the urine: lactose, pentose, fructose and galactose. Pentose and fructose are often found in the urine of healthy children who had consumed large quantities of fruit. These sugars and some amino acids may appear in the urine as a congenital metabolic disorder. False positive results of the tests may also be caused by the presence in the urine of large amounts of uric acid, creatinine, salicylates, terpin hydrate, antipyrin, amidopyrin, camphor and synthetic oestrogens which are often taken as contraceptives or for inhibition of lactation.

Polyuria in diabetes mellitus is of osmotic genesis. Its volume is determined approximately half by glucose and half by electrolytes and other hard substances contained in the urine: products of protein and nucleic acid breakdown (ammonium, uria, uric acid, creatinine, amino acids) and ketone bodies. In moderate polyuria, each gram of glucose 'sweeps' away with it 20 to 40 ml of urine. The severer the diabetes, the more manifest the polyuria and the

lesser is the amount of urine contained in each gram of glucose. This is precisely the explanation for the fact that the degree of glucosuria does not always correspond to the severity of polyuria.

Accumulation in the blood of large amounts of intermediate and end products of protein, fat and carbohydrate metabolism is attended by tissue dehydration. Dryness of the mouth and throat mucosa leads to thirst and polydipsia.

Marked hyperglycaemia and glucosuria with polyuria are often a component of the clinical picture of acromegaly, Itsenko-Cushing's disease, haemochromatosis and cranial trauma. The picture of diabetes mellitus is sufficiently well manifest only in the late periods of these diseases when the diagnosis of the principal suffering presents no difficulty.

Renal glucosuria is a harmless malady which is not attended by hyperglycaemia. Polyuria with glucosuria occurring in congenital functional disorders of the renal tubules is described in the next section.

Diabetes Insipidus

We group the following diseases under the term 'diabetes insipidus': congenital pituitary diabetes insipidus, acquired pituitary diabetes insipidus, and congenital nephrogenic diabetes insipidus. They are combined in one group on the basis of the assumption that all result from primary incapacity of the kidney to reabsorb water. The other functions of the kidney are normal in these diseases. It would be more true to state that modern methods of examination do not detect disorders of the other renal functions in these diseases. We conditionally use the term 'polyuria' to designate water metabolism disorders in some other congenital and acquired diseases.

We do not use the term 'diabetes insipidus' because the disorders of water metabolism are less sharply manifested in these diseases, as a rule, than in classical diabetes insipidus. Daily diuresis usually does not exceed three or four litres in these diseases and rarely reaches the volume always encountered in diabetes insipidus. Moreover, impaired water metabolism in these diseases is always secondary in character and is always attended by disorders of electrolyte metabolism, and often also by disorders of carbohydrate and protein metabolism.

The clinical manifestations of disturbances in electrolyte metabolism (muscle weakness and sometimes temporary paralysis of the respiratory muscles and the proximal muscles of the limbs, osteoporosis and osteomalacia, spontaneous bone fractures, nephro-

calcinosis, acidosis, excretion of alkaline urine, etc.) permit polyuria to be differentiated from diabetes insipidus.

We discuss involuntary polydipsia separately from the diseases mentioned above because there are grounds to believe that it is associated with primary affection of the thirst centre and not with impaired function of the renal tubules.

Pituitary diabetes insipidus. The clinical manifestations of pituitary diabetes insipidus are caused by deficient activity of the antidiuretic hormone produced by and stored in the supraoptic nucleus-neurohypophysis system. The disease is encountered at any age. Small epidemics of pituitary diabetes insipidus sometimes occur in India and China. It is a rare disease in the Soviet Union.

About 80 per cent of water filtrated in the glomerulus is reabsorbed in the distal part of the nephron. Deficient activity of the antidiuretic hormone leads to the loss of considerable amounts of water from the body. If the patient does not compensate these losses by drinking water or some other liquid, the concentration of hard substances in blood and other fluids increases rapidly, which may lead to the development of hyperosmolar coma. Thus, the principal mechanism of the disease consists in the inability of the kidney to retain water by concentrating the urine. The concentration power of the kidney in pituitary diabetes insipidus is fully restored under the effect of exogenous antidiuretic hormone, e.g. argenine-vasopressin.

The vivid and dramatic clinical picture of diabetes insipidus makes its diagnosis much easier. Polyuria, polydipsia and extremely low relative density of the urine are the principal signs. The onset of the disease is usually abrupt and most patients clearly remember the day and even the hour when polyuria and polydipsia had developed. The daily diuresis ranges from five to ten litres, reaching 15 to 20 litres in rare instances. Every two or three hours the patient drinks and excretes one to two litres of liquid. Polyuria leads to tissue dehydration. The patient's skin is dry and flabby, there is no perspiration, and salivation is sharply reduced. The constant dryness in the mouth is attended by unslacked thirst which is much stronger than the thirst experienced in diabetes mellitus.

The relative density of the urine in diabetes insipidus ranges from 1001 to 1005. If the patient is deprived of water, diuresis hardly decreases and the density of the urine slightly increases sometimes to 1010, but signs of severe dehydration appear. If the patient is unconscious and cannot ask for water death may occur from dehydration. Such a situation sometimes happens when diabetes insipidus develops suddenly after a neurosurgical operation or after injuries, for instance, after fracture of the base of the skull. Changes in the other internal organs in diabetes insipidus are mild or even not revealed

Pituitary diabetes insipidus may be *congenital* or *acquired.* Familial forms of diabetes are very rare. The first signs of familial diabetes appear in infancy or childhood. The most convincing proof of the hereditary transmission of diabetes insipidus was presented by Blotner in 1962 who described the development of this disease in seven (!) generations of one family. Pituitary diabetes insipidus the cause of which cannot be identified usually begins at a later age. According to some authors, this idiopathic form accounts for 15 to 40 per cent of all cases of diabetes insipidus.

All cases of diabetes insipidus developing soon after some acute infectious disease (influenza, measles, mumps, scarlet fever, diphtheria, meningitis, encephalitis) are generally regarded as *acquired (secondary) forms* of pituitary diabetes insipidus. Most convincing is the association of the disease with a skull injury, for instance with fracture of the base of the skull in the region of the sella turcica, with operations in this region, with thromboses, aneurysms of vessels, tuberculomas, gummas and with tumours of the diencephalo-hypophyseal area. Affection of these areas is also encountered in sarcoidosis, lymphogranulomatosis, leukaemias, amyloidosis, and some other diseases.

Pituitary diabetes insipidus is easily differentiated from diabetes mellitus. Its differentiation from nephrogenic diabetes insipidus and from involuntary polydipsia is a much more difficult problem. All these diseases are marked by polyuria, polydipsia, and low relative density of the urine. Pituitary diabetes insipidus is the only form of diabetes insipidus whose clinical manifestations are arrested completely or almost completely by agents containing active antidiuretic hormone.

Nephrogenic diabetes insipidus. An inflammatory process in the renal medulla impairs the capacity of the tubular epithelium to secrete the hydrogen ion into the urine. The reaction of the urine is shifted in the alkaline direction because of reduced excretion of ammonium and titrated acids. In hydrogen deficiency the sodium ions begin exchanging with potassium ions. Hypokaliaemia develops. In severer affection, the urine becomes alkaline while the epithelium of the distal tubules loses its power for concentrating the urine despite the sufficient content of the antidiuretic hormone in the blood. The clinical picture of nephrogenic diabetes insipidus develops. It may be congenital or acquired.

Congenital nephrogenic diabetes insipidus is an extremely rare disease. Isolated disturbed ability of the transport systems of the distal tubule to reabsorb water is the underlying factor. Continuous loss of considerable quantities of water leads to the development of polydipsia which must be differentiated from polydipsia and polyuria in pituitary diabetes insipidus and from involuntary polydipsia described below.

The disease is usually encountered in boys. The mother from whom the gene of nephrogenic diabetes insipidus is transmitted does not fall ill herself but the concentrating power of the kidneys is found to be diminished to some extent. The disease begins in the first months of the child's life and is manifested by extraordinary thirst and easily occurring attacks of dehydration. Urine is excreted in considerable amounts and is always more hypotonic than plasma. The recurrent attacks of dehydration, if severe and protracted, lead to damage of the cerebral cortical cells; as a result the mental ability of the child is impaired.

If death does not occur in childhood, the disease cannot be differentiated from pituitary diabetes insipidus by its clinical manifestations. Our patient with nephrogenic diabetes insipidus excreted seven to eight litres of urine daily, the density of the urine ranging from 1003 to 1004. A restriction of fluid intake increased the density of urine only to 1005. A longer restriction of water led, as in pituitary diabetes insipidus, to fever and hallucinations.

The tentative diagnosis of congenital nephrogenic diabetes insipidus is based on information concerning the onset of the disease in childhood, low osmolality of the urine, as well as on the results of trial therapy with natriuretic agents (hydrochlorothiazide, furosemide, uregit syn. ethacrynic acid). After these agents are prescribed, the volume of urine is reduced approximately by half while its relative density increases. A similar effect is produced by a hypoglycaemic agent chlorpropamide and an antispastic agent carbamazepine (tegretol). The final diagnosis is established only after it is disclosed that the patient is incapable of raising urine osmolality under the effect of vasopressin.

Polyuria in Disorders of Other Tubular Functions

Deficient reabsorption of water is only one of the causes of polyuria. Disturbances in some other tubular functions are also often attended by polyuria which must be differentiated from nephrogenic diabetes insipidus. There is as yet no generally accepted standard classification of these disturbances. Unfortunately, the physician is obliged to recognize diseases and to treat patients when unclear problems have still not been given a strict academic solution. This, to a certain measure, justifies the need to elaborate a working classification of the forms of polyuria. The classification suggested stems from the needs of practical medicine. It is based not on the mechanisms (although it proved impossible to ignore them completely) but on the causes of the development of polyuria.

Sodium, potassium, amino acids, glucose, phosphates, sulphates and urates are reabsorbed in an isotonic water solution in the proximal tubule of a normal nephron. Hydrogen and ammonium are also secreted here into the lumen of the tubule. The hydrogen ion binds with bicarbonate to form carbon dioxide and water. Carbon dioxide is reabsorbed and again converted to carbonic acid and bicarbonate under the effect of carbonic anhydrase. Uria and chloride are excreted according to the laws of simple diffusion.

Urine is concentrated in the distal tubule (the process is controlled by the antidiuretic hormone) and sodium reabsorption continues here. The rate of reabsorption is regulated by an ion-exchange mechanism the activity of which is controlled by aldosterone. Hydrogen and ammonium ions are also secreted here into the tubular lumen. Most of the hydrogen ions are excreted while bound with ammonium and the remaining part while bound with phosphates, creatinine and organic acid. Ammonium is the main acceptor of hydrogen in urine with pH below 5.5, and phosphates in urine with pH above this value.

Polyuria in pituitary diabetes insipidus must be differentiated from that in nephrogenic diabetes insipidus not only because of the difference in the developmental mechanisms, but also because their methods of treatment are different.

Fanconi's Syndrome (Adult Type)

Fanconi's syndrome is a very rare disease. It is inherited both as a recessive and as a dominant character. The hereditary form of the disease usually begins in childhood. The contemporary internist encounters Fanconi's syndrome in Waldenström's macroglobulinaemia, multiple myeloma, and other malignant gammapathies. This 'secondary' disease begins at middle or elderly age. Both the primary (hereditary) and the secondary (acquired) forms of the disease are manifested by amino-aciduria, phosphaturia and glucosuria. Hypokaliaemia develops because of diminished capacity for acidifying the urine. Impaired activity of the distal tubule in myeloma may be a consequence of hypercalciaemia which is often encountered in multiple myeloma. Disorders of calcium metabolism are manifested by rickets in childhood and by osteomalacia, osteoporosis, pain in the bones and spontaneous fractures in adults.

Pain in the bones is experienced by all patients with Fanconi's syndrome and almost always predominates in its clinical picture. Glucosuria and amino-aciduria are also constant signs of the disease. Polyuria occurs in about half the cases. It is usually mild. The daily diuresis is from three to four litres. Polyuria is always com-

bined with muscle weakness which is especially marked in the proximal segments of the limbs. Hypokaliaemia is the underlying factor of muscle weakness.

Glucosuria in Fanconi's syndrome is always of renal origin because the sugar level on an empty stomach is always normal in these patients, while the level of hyperglycaemia and the rate of the return of the glycaemic curve to the initial level in no way differ from the corresponding values in healthy individuals.

Polyuria in Fanconi's syndrome is mild and the disease is therefore never mistaken for diabetes insipidus. It usually must be differentiated from other diseases of the renal tubules or the cause of its origin must be identified. Recently Fanconi's syndrome more often proves to be a manifestation of dysproteinaemias, particularly of the most widely spread multiple myelomas and Waldenström's disease. Involvement of the kidneys is a frequent sign of these diseases. It is manifested by proteinuria, diminished concentrating power and moderate polyuria. Concomitant Fanconi's syndrome is diagnosed because of the appearance of the characteristic disorders, i.e. amino-aciduria, glucosuria and hypophosphataemia.

Tubular Acidosis

The concentration of hydrogen ions in the urine of a healthy person may be 800 to 1000 times their concentration in blood. The urine is acidified by the renal tubules. They lose this property in many diseases, the most commonly encountered of which are pyelonephritis, interstitial nephritis, hydronephrosis, polycystic kidneys, necrosis of the renal cortex, tuberculosis of the kidneys, Buttler-Albright's syndrome, and other diseases marked by hypokaliaemia and hypercalciaemia.

Although the clinical manifestations of tubular acidosis in children and adults are identical, childhood and adult forms of the disease are nonetheless generally distinguished. This is based on the assumption that tubular acidosis in infants is a congenital disease, whereas the adult form may be acquired or a continuation of the childhood disease.

The tubular acidosis syndrome may develop in any chronic atrophic or functional lesion of the renal cortex. Most cases of this syndrome in adults are caused by infection of the distal tubules. The findings of needle biopsy show that tubular acidosis is combined particularly often with interstitial nephritis and urolithiasis with stones in the renal medulla.

The increased tendency to the formation of stones in the kidneys in tubular acidosis is explained by disorders of calcium metabolism.

A patient with tubular acidosis continuously loses considerable

quantities of calcium in the urine, another consequence of which is osteoporosis. Osteomalacia develops in severer cases. Tubular acidosis should be suspected in every case of urolithiasis combined with osteomalacia.

In all cases of severe affection of the distal tubules, the urine reaction is shifted to the alkaline direction. The urine often becomes neutral or, in some cases, alkaline. This is sufficient for making a tentative diagnosis of tubular acidosis and calls for the need to test the capacity of the kidneys to acidify the urine. The simplest method is the prescription of no less than 0.1 mg/kg of ammonium chloride. In four to six hours after such a load, pH of the urine of a healthy person decreases to 5.0 to 4.5, but that of a patient with tubular acidosis remains on the initial level (it ranges between 6.5 and 7.0 in most cases). Polyuria and polydipsia occur in every case of tubular acidosis. Their degree is determined by the severity of the tubular affection.

Thus, the main diagnostic signs of tubular acidosis are as follows: inability of the kidney to produce acid urine after an ammonium chloride load; nephrocalcinosis with stones in the renal medulla; osteomalacia with pain in the bones; polyuria and polydipsia. The greater the degree of polyuria, the lower the relative density of the urine. Vasopressin prescription does not raise the relative density. The degree of muscle weakness is mainly determined by the degree of hypokaliaemia.

Affection of the proximal tubules is mainly encountered in children. The blood potassium and calcium content is normal in these patients. The reaction of the urine may be neutral or alkaline. It may become acid after ammonium chloride loading. Considerable loss of bicarbonates is the main cause of acidosis. Acidosis induced by affection of the proximal tubules occurs in Fanconi's syndrome (adult type). It may develop in any diffuse disease of the kidneys.

Hyperparathyroidism and Hypercalciaemia of Other Origin

Polyuria and polydipsia are early signs of hyperparathyroidism and are found in about 50 per cent of patients. Thirst may be so intense that patients drink up to 10 or 12 litres of water daily. The urine is often white because of a high content of calcium salts. The reaction of the urine is alkaline in more than half the patients. Although thirst in hyperparathyroidism is conspicous, it is nevertheless usually interpreted as a symptom of diabetes insipidus. The possibility of polyuria being associated with some other disease comes to mind only after unsuccessful treatment with adiurecrine (a dry preparation of the antidiuretic hormone).

Simultaneously with polyuria, and at times somewhat prior to it, the patient notices that he tires easily and experiences muscle weakness, particularly in muscles of the lumbar-iliac region and anterior tibial muscles. Weakness in these muscles progresses continuously. The patient lifts his legs with difficulty. Dorsal flexion of the foot is particularly sharply impaired. Pain in the feet also appears; the underlying factor is developing flatfoot. Loss of apparently healthy teeth and a sharp loss in body weight are also among the early signs.

Polyuria in hyperparathyroidism is combined with reduced concentrating power of the kidney. The relative density of the urine falls to 1002, while the reaction becomes alkaline in more than half the patients. The results of needle biopsy show that the underlying factors of the functional disorders are necrotic and necrobiotic changes of the epithelium of the ascending limb of Henle's loop and the distal tubules. Hyperparathyroidism is often complicated by the formation of stones in the kidneys which, in turn, often leads to the development of pyelonephritis.

The diagnosis of hyperparathyroidism is based on the constellation of the signs listed above, which serve as evidence only when combined with systemic osteoporosis and other signs of involvement of the bone system. Subperiosteal resorption of the proximal and middle phalanges of the fingers is a particularly common occurrence. Solitary or multiple cysts are seen in the long tubular bones if the process spreads to them. Affection of the spine is marked by considerably retarded growth. Blood calcium concentration and alkaline phosphatase activity are increased in almost all patients.

Hyperparathyroidism must often be differentiated from urolithiasis. Hyperparathyroidism complicated by nephrocalcinosis is characterized by thirst, polyuria, muscle weakness, and pain in the bones. Nephrocalcinosis in such cases is bilateral, as a rule. Recurrences of stone formation after surgery are typical of hyperparathyroidism, but are very rare in ordinary urolithiasis. These two diseases differ from each other in the reaction of the urine and the content of calcium and phosphorus in the blood and in the urine.

The *milk-alkali syndrome* sometimes develops when large doses of milk and soda or calcium carbonate are given in peptic disease. Treatment with calcium carbonate noticeably accelerates the development of the syndrome. Thirst and polyuria develop during the treatment and are soon joined by anorexia and loss of body weight. The blood calcium content increases. Stones sometimes form in the kidneys and even azotaemia develops. Neither osteomalacia nor osteoporosis occur in the milk-alkali syndrome; calcium salts are deposited not only in the kidneys, but in the cornea and the soft tissues of the fingers. When treatment is discontinued, calcium is resorbed from the metastases.

Hypercalciaemia is a characteristic sign of *sarcoidosis*, in which osteoporosis of the spine, cysts in the bones of the limbs and polyuria are also often found. Disorders of calcium metabolism with the development of polyuria are a frequent occurrence in *multiple myeloma*. These diseases are easily differentiated from hyperparathyroidism because of the concomitant disorders in calcium metabolism.

The prednisolone tolerance test makes it easier to differentiate hyperparathyroidism from sarcoidosis, multiple myeloma and the milk-alkali syndrome in many instances. Glucocorticoids reduce calcium absorption from the gastro-intestinal tract and thus reduce its content in the serum of healthy individuals and in patients with multiple myeloma and sarcoidosis. The blood calcium content in hyperparathyroidism does not change, or even increases sometimes under the effect of corticosteroids.

Conn's Syndrome and Hypokaliaemia of Other Origin

The combination of polyuria with arterial hypertension and muscle weakness was distinguished as a separate syndrome by Conn. In about 90 per cent of cases it is induced by adenoma of the adrenal glomerular zone. An aldosterone secreting tumour may be unilateral or bilateral. In some cases the picture of the syndrome is caused by micronodular hyperplasia of the adrenal cortex. The disease occurs predominantly among females. Its initial manifestations are not typical and consist in rapid fatiguability and usually moderate arterial hypertension. In far-advanced cases the patients complain of polyuria, polydipsia, rapid fatiguability and attacks of rigidity. Paraesthesia and tonic spasms in the muscles of the face and limbs are often encountered.

Aldosterone hypersecretion is attended by hypokaliaemia which, if of a considerable degree, leads to the development of vacuolar degeneration of the renal tubules. As in tubular acidosis, the kidney loses its ability for urine concentration. The reaction of the urine is shifted in the alkaline direction and becomes alkaline in severer cases. In our patients, the daily volume of urine was as high as three to six litres and its relative density ranged from 1003 to 1012. Polyuria in Conn's syndrome, like in the other nephrogenic forms of polyuria, is resistant to treatment with the antidiuretic hormone. The prescription of vasopressin has no effect on the volume of the urine and does not raise its relative density.

Muscle weakness is slight at the onset of the disease and the patient simply thinks that he is tiring easily. Brief attacks of weakness develop later. During such lapses of strength the patient may

suddenly fall because of atonia of his lower limb muscles. A much more frequent occurrence are attacks of muscle weakness in the upper limbs, during which the patient cannot hold a cup or a plate in his hand. At first he attributes this to awkwardness. With the advance of the process, muscle weakness becomes permanent. It is most marked in the proximal muscles of the limbs, but may also spread to the muscles innervated by the cranial nerves. Paresis of the smooth muscles of the intestine leads to abdominal distension. Muscle weakness may last from a few minutes to several weeks during which the patients can hardly move about the room. At times, they cannot even tend for themselves.

Arterial pressure is almost always elevated. The malignant hypertension syndrome with severe headache, retinopathy and characteristic changes in the heart often develops. Hypertensive crises occur sometimes; they are evidently induced by pressure of the tumour on the adrenal medulla. Hypokaliaemia, increased excretion of aldosterone in the urine and its increased content in the blood, and the absence of renin in the blood are characteristic laboratory signs. Retropneumoperitoneum is applied to localize the tumour.

In some cases of Conn's syndrome muscle weakness is so severe that hyperparathyroidism is suspected in the patient. It is relatively simple to make the differential diagnosis between these diseases. In Conn's syndrome arterial pressure is usually very high, the blood calcium content is normal, and there are no bone changes characteristic of hyperparathyroidism.

Polyuria with four or five litres of urine excreted daily is often encountered in thyrotoxicosis. The arterial pressure in these patients may be normal or elevated. Systolic hypertension and increased content of thyroid hormones in blood are typical signs. Muscle weakness in thyrotoxicosis may be so severe that the patient is unable to get up from bed unassisted. An enlarged thyroid gland, tachycardia, and ocular symptoms make the diagnosis of thyrotoxicosis easier.

It is much more difficult to distinguish Conn's syndrome marked by generalized muscle weakness from periodic paralysis, the paroxysmal form in particular. In considering the differential diagnosis between paroxysmal myoplegia and Conn's syndrome, special attention should be focused on the results of arterial pressure measurement: it is almost always elevated in Conn's syndrome but usually normal in periodic paralysis. Hypokaliaemia is permanent in Conn's syndrome but transitory in periodic paralysis; it is detected during an attack of myoplegia but the blood potassium content is normal in periods clear of attack. Polyuria and low relative density of urine are considered to be typical signs of Conn's syndrome and are not encountered in periodic paralysis.

Other Diseases of the Kidneys

Distension of the inner cavities of the kidney, i.e. the pelvis and the calyces with atrophy of the parenchyma, is called **hydronephrosis.** Atrophy develops as a consequence of high pressure exerted by the urine on the renal tissue and as a consequence of disturbed renal circulation. The less vascularized medulla atrophies first. In the cortex, which has a richer supply of vessels, the atrophic process sets in later and develops slower.

Hydronephrosis may be congenital or acquired. The acquired variant is usually encountered in women taking hormonal contraceptives, in retroperitoneal fibrosis, and in males with tumours of the prostate.

The kidney in hydronephrosis is enlarged and its surface is nodular. The renal tubules are distended, particularly in their distal parts. With the development of the atrophic process, the functions of the distal tubules are progressively impaired. Processes of water reabsorption and urine acidification are disturbed first; this is attended by the development of polyuria. The daily volume of urine reaches four to eight litres in some cases. Polyuria is commonly attended by thirst. The relative density of urine falls to 1012-1005 and its reaction is shifted in the alkaline direction. Sometimes it becomes neutral. Tubular acidosis develops in severer cases and the urine turns alkaline. Urine retained in the distended cavities of the kidney is often infected and interstitial nephritis develops in attendance to hydronephrosis.

Asymptomatic hydronephrosis is very rare. Most patients with hydronephrosis complain of heaviness and dull pain in the abdomen and small of the back caused by pressure of the enlarged affected kidney on the adjoining organs. Attacks of renal colic develop if urine drainage is arrested. These attacks are attended by rapid enlargement of the kidney and a decrease in the volume of urine. Polyuria appears as soon as the attack ceases. A great number of leucocytes are found in the urine in hydronephrosis complicated by infection. Exacerbation of the infection is accompanied by fever. Hydronephrosis is sometimes complicated by acute papillitis. The findings of contrast X-ray studies help to establish the diagnosis.

Polyuria and reduced relative density of the urine are constant signs of far-advanced **pyelonephritis** and so-called **analgesic nephropathy** whose clinical picture resembles that of chronic pyelonephritis in many cases. Diffuse or localized **interstitial nephritis** is demonstrated histologically in both diseases. The inflammatory pro-

cess leads to gradual sclerosis of the renal parenchyma and the formation of a contracted kidney. Both diseases are sometimes complicated by necrotic papillitis.

Polyuria in these diseases is usually mild. The daily volume of urine rarely exceeds four or five litres. The gradual diminution of tubular function leads to the development of tubular acidosis. The urine turns neutral or alkaline and its relative density is low. Chronic pyelonephritis is often complicated by arterial hypertension. Analgesic nephropathy develops under the effect of acetophenetidin which is a component of many headache relieving agents. It is generally believed that affection of the kidneys usually develops in patients who had taken at least two kilograms of acetophenetidin. Questioning the patient about the intensity of headache and when he had begun suffering from it, and the methods of its treatment, may make it easier to identify the cause of polyuria and polydipsia.

Microcystic degeneration of the renal medulla is encountered almost exclusively among individuals with light-coloured or red hair. The slowly developing dysfunction first of the distal tubules leads to hyposthenuria which is soon replaced by isosthenuria. The daily diuresis grows gradually. Polyuria is attended by diminished power of acidifying the urine. Tubular acidosis develops usually in combination with reduced renal capacity for sodium reabsorption. In this stage of development, microgranular degeneration of the renal medulla resembles 'nephritis with sodium loss'. Patients die young from chronic renal failure.

Polyuria and polydipsia are commonly encountered signs of polycystic kidney disease which is usually already far-advanced. Cysts of various size are found both in the cortex and in the medulla. Some communicate with the lumen of the tubules, others are isolated. The formation of the cysts is attended by atrophy of the renal tissue. Infection of the cysts is complicated by the development of interstitial nephritis. Not infrequently, the disease is complicated by arterial hypertension.

The first signs of polycystic kidney disease usually appear between the ages of 20 and 40. With the gradual advancement of the disease, the relative density of the urine decreases and polyuria becomes more marked. The terminal stage of chronic renal insufficiency usually develops ten years after the onset of polyuria.

Involuntary Polydipsia

The protracted discussion on the role of the hypothalamus-hypophysis system in regulating the constancy of the body's inner medium terminated in the recognition that diabetes insipidus is a

consequence of primary disturbance in water reabsorption in the renal tubules whereas involuntary polydipsia is a consequence of primary stimulation of the specific receptors of the thirst centre which differ from the receptors of the antidiuretic hormone detecting changes in serum osmolality. Stimulation of the thirst receptors leads to 'primary polydipsia' whose main defect consists in the appearance of a sensation of thirst though the content of fluid in the body is normal.

The disease occurs in middle-aged females with mental instability as a rule. Polyuria and polydipsia are its main signs. Daily diuresis reaches 8-12 litres. As in diabetes insipidus, the urine is clear and its relative density ranges from 1001 to 1005. Involuntary polydipsia is never complicated by tubular acidosis or azotaemia and therefore is differentiated only from various types of diabetes insipidus.

In considering the differential diagnosis between these diseases it would be well to remember de Wardener's concept to the effect that involuntary polydipsia is a grave mental disease which is accompanied by other disorders of the patient's personality and behaviour. Increased thirst and polyuria in all cases of involuntary polydipsia develop in attendance to an already existing psychoemotional instability. Diabetes insipidus, on the contrary, begins with polyuria, while emotional instability is always secondary in character. It may develop only some time after the onset of the disease.

The activity of the kidney concentrating mechanism is impaired in a person who drinks much water for a great length of time. This creates difficulties in interpreting the results of numerous laboratory tests which have been suggested for differentiating involuntary polydipsia from diabetes insipidus.

Deprivation of the patient of water is the simplest laboratory test. Among the numerous variants of this test, the most reliable is that of repeated weighing of the patient at intervals of one or two hours and measuring the volume and relative density of the urine. The test is continued until the patient loses 3 or 4 per cent of body weight, but usually for no longer than 24 hours. In a healthy person the volume of urine reduces to 30 ml/h in six to ten hours after the beginning of the test, while the relative density of the urine grows to 1020 or more. In patients with diabetes insipidus, the volume of urine does not reduce during the test and the relative density remains at a level of 1001 to 1005. Urine osmolality remains low until dehydration occurs. In patients with acquired diabetes insipidus, the clinical signs of dehydration occur only when the urine concentration reaches a relative density of 1008 to 1014.

The test with water deprivation helps in verifying the diagnosis of diabetes insipidus in most cases, but its results are often insufficiently convincing for differentiating diabetes insipidus from involuntary polydipsia because the urine concentrating power of the kidney of these patients is diminished.

The test with intravenous infusion of sodium chloride is based on the same principle of examining the patient by increasing blood osmolality. The test begins (without fail!) with intravenous infusion of isotonic glucose solution

at an approximate rate of 8-10 ml/min so as to induce copious diuresis. When the rate of urine flow reaches 5-6 ml/min, the glucose solution is replaced by 2.5 per cent sodium chloride solution infused for 45 minutes at a rate of 0.25 ml/min/kg. The urine is collected and measured every 15 minutes.

If the functions of the neurohypophysis and kidneys are normal, infusion of hypertonic sodium chloride solution reduces the volume of the urinary flow usually to 25 to 20 per cent of the volume established during glucose infusion. The results of the test should be appraised in the light of the clinical picture.

Pituitary preparations available are tested biologically and noticeably differ in activity. Crystalline preparations have appeared lately, but even after their prescription it is extremely difficult to differentiate pituitrin-induced diabetes insipidus from the nephrogenic form. Protracted polydipsia and polyuria noticeably reduce the concentration power of the kidneys. This function also remains diminished after a single administration of hyperosmotic sodium chloride or pituitrin solution. It was demonstrated on models of congenital pituitrin-induced diabetes insipidus that this function is restored after approximately three weeks of continuous use of vasopressin.

In studying the problem of the differential diagnosis of polyuria, de Wardener came to the conclusion that the urine of a healthy person becomes more concentrated after dehydration than after vasopressin. The concentration of urine of a patient with diabetes insipidus is higher after medication with vasopressin than after dehydration. Two important diagnostic conclusions proceed from this: (1) if the concentration of urine after dehydration is higher than after the use of vasopressin alone, one may speak of normal secretion of the antidiuretic hormone in the person examined, irrespective of the values of urine osmolality (relative density); (2) if urine concentration is higher after deprivation of liquids than after the use of vasopressin, the ability to secrete the antidiuretic hormone is impaired irrespective of the value of the relative density. Following these criteria and with due account for the clinical picture of the disease de Wardener almost always successfully differentiated involuntary polydipsia from diabetes insipidus.

Supplement XXIV-1

The Causes of Polyuria and Polydipsia

1. Diabetes mellitus.
2. Diabetes insipidus.
   - Congenital pituitary.
   - Acquired pituitary.
   - Congenital nephrogenic.

3. Symptomatic tubular polyuria.
   - Fanconi's syndrome (adult type).
   - Tubular acidosis.
   - Hyperparathyroidism.
   - Milk-alkali syndrome.
   - Sarcoidosis.
   - Multiple myeloma.
   - Conn's syndrome.
   - Thyrotoxicosis.
   - Paroxysmal myoplegia.
   - Hydronephrosis.
   - Pyelonephritis.
   - Analgesic nephropathy.
   - Interstitial nephritis.
   - Polycystic kidney disease.
   - Microcystic degeneration of the renal medulla.
   - Urolithiasis.
4. Involuntary polydipsia.

Chapter XXV

Purpura

The term 'purpura' designates capillary haemorrhages occurring spontaneously or under the effect of minor injuries.

Punctate haemorrhages (petechiae) and livid spots on the skin caused by extravasations of blood (ecchimoses) are usually localized in the skin and mucous membranes. They differ noticeably from one another in size. On coalescing, they may form quite extensive ecchimoses with fantastic boundaries. Bleeding from the mucosal capillaries into the body cavities and onto its surface sometimes proves to be the only manifestation of the syndrome. Bleeding from the nose and from the gums is most common. In other organs purpura is rare.

Damage to the capillary wall in the body of a healthy man is attended by activation of the protective haemostasis mechanism. The blood platelets accumulate at the site of the defect in the epithelial tissue. On interaction with collagen of the adjacent connective tissue, serotonin and adenosine diphosphate are produced within the platelets; under the effect of these substances, the platelets glue together forming an aggregate which loosely plugs the lumen of the capillary. These primary thrombi are almost completely formed of platelets and a small admixture of red cells.

Simultaneously with the process described, tissue thromboplastin is released in the neighbourhood of the injured capillary. Under its effect a small amount of thrombin forms between some of the platelets in the aggregate. The loose aggregate of platelets contracts due to the effect of thrombin and firmly blocks the anatomical defect in the capillary.

Although the mechanisms of blood coagulation contribute to the interaction of the platelets and the wall of the injured capillary, they have no decisive effect on the course of the processes described above. The entirety of these processes is often called the mechanism of primary haemostasis, or, figuratively speaking, the 'haemostatic nail'. Disorders of this mechanism underlie the clinical manifestations of purpura.

In practice, one constantly experiences the need to distinguish purpura from haemorrhagic diatheses resulting from disorders of blood coagulation mechanisms.

The complex character of purpura pathogenesis, i.e. the existence of diseases in which primary haemostasis and processes of blood coagulation are simultaneously impaired, makes it clear why the precise diagnosis of the separate clinical forms of haemorrhagic diathesis may be established only in large haematological laboratories. Nonetheless, clinical experience accumulated to date permits the main types of haemorrhagic diathesis to be distinguished from one another in most cases before all comprehensive laboratory studies are undertaken.

Purpura is usually manifested by petechiae and ecchimoses which occur in a previously healthy person as if spontaneously in no as-

sociation with a preceding trauma. Purpura is sometimes preceded by an acute infectious disease, or medication with some drugs. Its association with other diseases is determined in many cases. Purpura begins as an acute disease and, in many instances, disappears spontaneously some time after. Sometimes it takes a chronic course with periods of exacerbations and remissions. No tendency to bleed is found among the relatives of a purpura patient as a rule.

Abnormal bleeding due to disorders of blood coagulation differs from purpura in that it is discovered from childhood in most cases and lasts throughout life. Haemorrhages occur after a more or less serious injury as a rule. It is sometimes revealed that the patient's relatives suffer from similar haemorrhages.

Disorders of blood coagulation are usually manifested by deep haematomas, haemarthrosis or extensive intramuscular extravasations. In purpura, petechiae and ecchimoses are found only in the skin and mucous membranes. Haemarthrosis does not develop. The fact that purpura is encountered more often in females while disorders of coagulation occur mostly among males is also of certain significance.

Bleeding after tooth extraction or tonsillectomy may last two or three days in patients with impaired blood coagulation. Recurrence of bleeding that had ceased is particularly characteristic. No protracted bleedings or recurrences are encountered in purpura. Petechiae and ecchimoses in purpura are commonly found in great numbers in areas where the skin is compressed with a belt, girdle or suspenders. In impaired blood coagulation there is no such regular distribution of haemorrhages.

Females with a particularly tender skin, mainly blondes, suffer indefinitely from ecchimoses which easily appear and disappear, particularly on the lower limbs. Additional methods of examination may prove to be helpful when clinical examination yields no definite answer. The simplest methods may be easily applied at the patient's bedside.

Bleeding from the lobule of the ear after puncture with Francke's needle with the blade advanced by 4 mm lasts more than four minutes in a healthy person. It is generally accepted that this period does not change in disorders of coagulation, but is noticeably prolonged in purpura. Unfortunately, this is not always the rule. According to some authors, abnormally prolonged bleeding occurred in two thirds of patients with purpura caused by impaired function of the blood platelets and only in half the patients with purpura syndromes of other origin. Compression of the arm for five minutes with the cuff of a Riva-Rocci sphygmomanometer under pressure that is above diastolic and below systolic leads to the appearance of only solitary petechiae in the skin of the forearm of a healthy person. It is generally accepted that the results of this test are al-

ways positive in purpura. But the number of petechiae was considerably increased only in 13 per cent of patients who were examined. It is therefore obvious that the diagnostic value of the additional simple methods of examination is limited.

The character of the vascular affection will be assessed at the patient's bedside more accurately if the judgement is based on the results of physical examination and questioning and not on the results of tests for the bleeding time and capillary fragility.

There are marked differences in the incidence and causes of purpura in children's departments and in departments for internal diseases in adults. Purpura is encountered much less frequently in departments for adults. Most cases (Supplement XXV-1) are caused by anatomical and toxic affection of the bone marrow. Myeloproliferative syndromes take first place. In our experience, purpura was particularly often the first clinical manifestation of myeloproliferative leukaemia. Infiltration of the bone marrow with tumours or metastases was also a frequent cause of purpura.

Purpura developing as a consequence of the toxic effect of infectious diseases and drugs on the bone marrow is encountered in adults less frequently than purpura caused by anatomical lesion of the bone marrow. Purpura in such cases is merely one of the syndromes of a systemic disease and rarely predominates in the clinical picture. Purpura of unknown aetiology (thrombocytopenic or simplex) is quite rare among adults.

Purpura may be diagnosed as idiopathic only after commonly encountered and rarer causes are ruled out. There is a great number of diseases which rarely cause purpura. Listing them will in no way lessen the difficulties of their identification.

Purpura is mostly encountered in combination with thrombocytopenia and the blood platelet count is therefore the first diagnostic measure in this syndrome. According to the results of the test, thrombocytopenic and vascular (non-thrombocytopenic) forms of purpura are distinguished.

Thrombocytopenic Purpura

One µl of blood of a healthy person contains $2 \cdot 10^5$-$3 \cdot 10^5$ of blood platelets. Purpura usually develops when the platelet count is below $5 \cdot 10^4$ per 1 µl of blood. In some cases it may be absent when the platelet count falls to $2 \cdot 10^4$ and even to $1 \cdot 10^4$ per 1 µl.

Thrombocytopenia is usually a consequence of deficient thrombocytopoiesis or accelerated destruction of platelets in the patient's

body. Other causes are rarely encountered in departments for internal diseases.

The differentiation of the causes of thrombocytopenia in Supplement XXV-2 is artificial to a great measure, because thrombocytopenia in a given patient may be of complex origin. For instance, thrombocytopenic purpura in carcinoma metastasis may be a consequence not only of a simple reduction in the number of megakaryocytes due to the effect of bone marrow infiltration by the tumour cells but of the parallel development of autoimmune platelet lysis. The results of sternal puncture or, still better, the results of trephination biopsy show in such cases the importance of the first of these factors and simultaneously demonstrate the practical expediency of the entire classification.

Purpura consequent upon deficient thrombocytopoiesis is often encountered in myeloid metaplasia of the bone marrow, in metastasis of tumours to the bone marrow, in multiple myeloma, and in myelofibrosis. Radioactive radiation and some chemotherapeutic agents applied in the treatment of new growths and some other diseases sometimes inhibit the function of all bone marrow germs and sometimes lead to the predominant or selective affection of the megakaryocytes. Thrombocytopenia in the latter cases is the earliest sign of a myelotoxic effect. Deficient thrombocytopoiesis may be encountered in combination with hypoplasia of the erythrocytic and myeloid germs of the bone marrow (e.g. in Fanconi's syndrome, hypoplastic anaemia, vitamin B_{12} and folic acid deficiency, azotaemia). Congenital deficiency of megakaryocytes in the bone marrow is extremely rare and is always combined with other developmental anomalies.

Trephination biopsy or sternal puncture permits the association of thrombocytopenic purpura with the state of bone marrow haematopoiesis to be determined. Disorders of thrombocytosis are displayed by a decrease in the number of megakaryocytes in the bone marrow aspirate, or their disappearance. Of no less diagnostic importance are other changes in the bone marrow specific of each of the diseases listed. A normal state of bone marrow haematopoiesis indicates that the decrease in the number of blood platelets is evidently due to their destruction outside the bone marrow.

It is assumed that platelets take part in immunological reactions by adsorbing complexes of some antigens on their membrane. Infusion of gamma globulin fraction of blood taken from a patient with thrombocytopenic purpura is often attended by a marked decrease in the blood platelet count in a healthy recipient. On the basis of these factors it was suggested that drug-induced and some other forms of thrombocytopenic purpura are associated with immunological mechanisms.

Werlhof's Disease

Werlhof's disease is the most widely known representative in this group of thrombocytopenic purpura. It is encountered in two forms, acute and chronic. Both forms are marked by a normal or increased number of megakaryocytes in the bone marrow and no involvement of the spleen in the morbid process.

Acute thrombocytopenic purpura occurs as a rule in children, boys and girls. Intensive purpura appears suddenly in a child or adolescent who has no history of haemorrhagic diathesis. In 90 to 95 per cent of patients, purpura disappears spontaneously in 12 to 14 days. Only a small number of patients develop chronic thrombocytopenia. The spleen is not palpated in these patients, the number of megakaryocytes in the bone marrow increases.

Acute thrombocytopenic purpura often sets in one or two weeks after recovery from a respiratory infection. It is possible that in such cases thrombocytopenia is not idiopathic (as it is shown in Supplement XXV-2), but is of a secondary character, developing due to the removal from the blood flow of a large number of platelets together with the antibody-antigen complexes adsorbed on their surface. Most clinicians do not agree with this point of view and consider acute thrombocytopenic purpura to be a form of Werlhof's disease, and leave the problem of its pathogenesis open to question.

Purpura neonatorum is encountered in the first two or three days of life. The haemorrhagic phenomena cease after this period but thrombocytopenia persists sometimes for two or three months. The condition develops in infants born of mothers suffering from Werlhof's disease.

The **chronic form of Werlhof's disease** begins insidiously. Its incidence among young girls and women is three- to fourfold that among young boys and men. In typical cases, menstrual bleedings in a girl gradually intensify, the tendency to develop ecchimoses even after trivial injuries grows, and protracted haemorrhages occur after tooth extraction or after other minor surgical operations. The platelet count falls to $1 \cdot 10^5$-$5 \cdot 10^4$ (100 000-50 000) per 1 μl. The activity of the megakaryocytic bone marrow germ is often increased. The spleen is not enlarged. Remissions are replaced by recurrences from time to time for many years. Recurrences develop characteristically in the premenstrual period. Enlargement of the spleen makes the diagnosis of the chronic form of Werlhof's disease questionable.

The listed laboratory and clinical signs are always encountered in the chronic form of Werlhof's disease, but in order to make the diagnosis, these signs must be detected and the possibility of their connection with other diseases (see Supplement XXV-2) which can be complicated by thrombocytopenic purpura must be ruled out.

It is particularly important to rule out **drug-induced purpura.** This is achieved by discontinuing all drugs which had been given to the patient. If the patient's condition does not allow all the drugs to be discontinued, they must be replaced by others which produce a similar pharmacological effect but have a different chemical structure. The clinical manifestations of drug-induced thrombocytopenic purpura disappear usually no later than two or three weeks after the drug which had caused it is discontinued.

High differential diagnostic significance is attached to the character of the patient's reaction to trial therapy. After treatment with high doses of steroid hormones (e.g. 40 to 60 ml of prednisolone daily or equivalent doses of its analogues), the number of blood platelets increases in the first two or three weeks in most patients with the chronic form of Werlhof's disease. The disease recurs in most patients one to four weeks after steroids are discontinued. After splenectomy, this recurrence in about 70 per cent of cases is replaced by a protracted or permanent remission.

Drug-induced thrombocytopenic purpura occurs in a sensitized patient due to the effect of an agent which he had tolerated well previously. The onset of drug-induced purpura is always abrupt. Its duration is determined by the rate of the breakdown of the drug in the body. This regular feature is clearly confirmed in follow-up of purpura caused by cardiac glycosides. Purpura disappeared in our patients two or three days after toluzine had been discontinued. Digitoxin breaks down slower in the body than toluzine. Purpura induced by digitoxin preparations (acedoxin, acylanid) disappeared no earlier than two weeks after they had been discontinued.

Purpura cannot be considered induced by a drug if it did not disappear two to three weeks after the drug was no longer given. Any drug may induce purpura and to identify the cause it is therefore necessary to remove all drugs which the patient had received. Many patients fail to inform the doctor that they had taken acetylsalicylic acid, soporifics or headache-relieving tablets for many years considering them to be absolutely harmless. Long-term follow-up of patients with chronic disease allows for stating that purpura may even be induced by drugs which had been tolerated well for many years (e.g. cardiac glycosides). Supplement XXV-3 lists drugs which cause thrombocytopenic purpura.

The clinical signs mentioned above provide grounds for making a tentative diagnosis of drug-induced purpura. The final diagnosis is based on their combination with delayed clot retraction, growth of the platelet third factor in the patient's blood, and complement-fixation reaction. These tests are carried out in specially equipped laboratories.

Quite often thrombocytopenic purpura occurs a few days after **blood transfusion.** The disease develops because antithrombocytic

complement-fixating isoantibodies appear in the recipient's blood after transfusion of blood containing platelets incompatible with the recipient's platelets in antigenic composition. The disease may last two or three weeks and terminate spontaneously.

Thrombocytopenic purpura is found in approximately 10 per cent of patients with **systemic lupus erythematosus.** It is sometimes the earliest clinical manifestation of this disease. Thrombocytopenic purpura is likewise encountered in **scleroderma, lymphatic leucosis, lymphosarcoma, and autoimmune haemolytic anaemia.** The combination of thrombocytopenic purpura with autoimmune haemolytic anaemia is called Evans' syndrome. The spleen in this syndrome is not enlarged and the direct Coombs' test is positive.

Intravascular coagulation occurs in many clinical conditions. The arising clinical pictures are designated the 'defibrination syndrome' or 'utilization coagulopathy'. A great number of blood platelets are spent for the formation of procoagulants in blood in this syndrome, as a result of which marked thrombocytopenia develops. Haemorrhages of various severity are found in some cases of this syndrome and the formation of small intravascular thrombi without haemorrhages in others. The syndrome is encountered after transfusion of incompatible blood or snakebites, in haemorrhagic shock, leukaemia, carcinoma, sepsis (purpura fulminans) and in intolerance of some drugs.

Thrombocytopenic purpura with multiple thromboses of small vessels was first described by Moschcowitz in 1925. Fever, haemolytic anaemia, thrombocytopenia, and affection of the kidneys and central nervous system are the characteristic signs. There is a normal content of megakaryocytes in the bone marrow. The onset is abrupt and the disease terminates in one to six weeks in death or in a clinical picture of severe haemorrhages, anaemia and thrombi in the vessels of the brain. The diagnosis is made with difficulty because of the multisystemic affection. The histological picture of the vessels (hyalinosis and thrombosis of the arterioles) gives grounds to regard thrombotic thrombocytopenic purpura as a generalized Sanarelli-Schwartzmann reaction.

Thrombocytopenia in acute virus (measles, rubella and other exanthemas) **and bacterial** (enteric fever, bacterial endocarditis) **diseases** is probably a consequence of the toxic effect of the causative agent on the megakaryocytes. Nor can one exclude the possibility that the number of platelets decreases because of phagocytosis. The blood platelet count returns to normal levels when the patient recovers from the principal disease.

Massive blood transfusion and prolonged extracorporeal circulation often lead to moderate or marked thrombocytopenia. It results from the dilution of the recipient's blood with a large volume

of blood substitutes or with blood containing a small number of platelets.

In the body of a healthy person about one third of platelets is contained in the spleen. The remaining circulate in blood. A considerably enlarged spleen may contain up to 90 per cent of the total number of platelets. The content of platelets in the peripheral blood decreases. This is a particularly constant occurrence in Gaucher's disease, sarcoidosis, lymphosarcomatosis, and congestive and other splenomegalies. Similar sequestration of platelets takes place in large hemangiomas. The causes of thrombocytopenia in heat stroke, macroglobulinaemias, premature detachment of the placenta, burns, and some other diseases are not known.

Non-thrombocytopenic Purpura

It was comparatively recently that all purpuras in patients with a normal number of blood platelets were generally attributed to a lesion of the wall of the small vessels. The mechanism of the development of some of these purpuras has been identified to date and their association with functional deficiency of blood platelets and with congenital or acquired lesions of the vascular wall has been demonstrated (Supplement XXV-4).

Practitioners most often encounter cases of purpura simplex. It usually occurs in adult females, particularly in blondes. The lower limbs are mainly involved. Small ecchimoses form with no apparent cause, disappear in six to eight days and are soon replaced by others. The appearance of the ecchimoses is preceded by a burning sensation. The cause of purpura simplex is not known. All laboratory tests for haemostasis are normal in these patients. Biopsy of the affected skin areas shows no changes in the vessels.

Purpura in haemorrhagic vasculitis (Schoenlein-Henoch anaphylactoid purpura) is only a sign of generalized affection of the arterioles and capillaries. Angiitides with necrosis of the walls and obstruction of the small vessels lead to the formation of extravasates. The perivascular inflammatory infiltrates are sometimes developed to such an extent that they cause oedema of the skin and mucous membranes.

The mechanism of primary haemostasis in haemorrhagic vasculitis is not impaired. The number of platelets is sometimes slightly reduced but they always function normally. The bleeding time and the mechanisms of blood coagulation are normal. The Konchalovsky-Rumpel-Leede phenomenon and the pinch sign are often negative.

Lesions of the skin and mucous membranes occur almost in all cases of haemorrhagic vasculitis. Ecchimoses, ranging in size from a pinhead to a patch 1 or 2 cm in diameter are first isolated, but

later they often coalesce. The haemorrhages are usually elevated above the skin and their centre undergoes necrosis in severe cases. The typical papular haemorrhagic eruption is sometimes preceded by urticaria. The lower limbs and the buttocks are involved as a rule. Lesions occur much less frequently on the upper limbs, face and trunk. Predominant localization of the eruption on the extensor surfaces of the limbs and around the large joints is a characteristic sign.

Haemorrhagic vasculitis is usually encountered in children but may develop for the first time at any age. In distinction from thrombocytic purpura, haemorrhagic vascultitis is marked by simultaneous appearance of eruptions on the skin and mucous membranes and involvement of the joints, gastro-intestinal tract, kidneys, heart and central nervous system.

The knee and ankle joints are usually affected. Periarticular swelling sometimes occurs. Movements at the joints are restricted because of pain which is felt for about a week. There is a characteristic discrepancy between the severity of pain in the joints and the extremely poor objective signs of their inflammation. Pain in the joints and swelling of periarticular tissue are not encountered in thrombocytopenic purpura. The final diagnosis in doubtful cases is based on the results of biopsy. Haemorrhagic vasculitis is marked by the typical changes in the small skin vessels described above.

Abdominal pain is found in approximately half of the sick children. It has the character of colic. Vomiting often occurs at the peak of pain. It is presumed that the pain is caused by oedema developing in association with haemorrhages into the intestinal wall. Bleeding into the gastro-intestinal tract may be attended by bloody vomiting and melaena.

Haematuria, proteinuria, and increased arterial pressure are encountered most commonly in children over six years of age. Most patients recover fully, but in about 20 per cent these changes persist for many years. In cases followed up over long periods, V. A. Nasonova discovered clinical and histological signs of chronic nephritis. Microhaematuria is sometimes encountered in Werlhof's disease, but it always disappears during a remission.

Generalized affection of the small vessels with haemorrhage into the skin, mucous membranes and other organs also occurs in thrombocytopenic purpura (Moschcowitz's disease). In distinction from Moschcowitz's disease, haemorrhagic vasculitis usually follows a favourable course with subfebrile temperature and terminates in recovery in three or four weeks. The recovery may be complete if there is no involvement of the kidneys. Recurrences of this disease also have a favourable prognosis. They develop in approximately 50 per cent of patients. Moschcowitz's disease is marked by high fever, haemolytic anaemia, thrombocytopenia, often by a picture

of recurrent cerebral circulatory disorders, and has an unfavourable prognosis. No thromboses of the cerebral vessels occur in haemorrhagic vasculitis as a rule.

Haemorrhagic vasculitides of drug origin were encountered in our practice particularly often in prolonged treatment with thiazide preparations. As one can see from published data, many drugs listed in Supplement XXV-3 may lead to proliferation of the endothelium of the small vessels and plugging of their lumen. The haemorrhagic phenomena are usually mild and disappear completely soon after the drug is discontinued. The number and functioning of the platelets may be normal.

Purpura resulting most probably from sensitization to the person's own red cells may also be included in this group. It occurs among women with signs of severe hysteria. Haemorrhages which are usually not very severe occur as nasal bleeding, menorrhagia, and haematuria. Haemorrhages from the gastro-intestinal tract have also been described. The skin lesions form on the extensor surface of the upper and lower limbs. Pain is felt at first, and swelling and erythema with ecchimoses on its periphery appear at this site a few hours later.

The described picture of purpura is called the syndrome of sensitization to one's own red cells because its manifestations are sometimes reproduced by intracutaneous injection of 0.1 ml of blood taken from the patient's vein.

Purpura in scurvy is not an early sign of the disease. It has a characteristic appearance, and forms first on the lower limbs. Punctate ecchimoses are always arranged around the follicles. They coalesce later to form petechiae of various size and shape. Other forms of haemorrhages (intrapleural, intramuscular, subperiosteal) are often found simultaneously with purpura. Sharp tenderness of the lower limbs to palpation results from intramuscular and subperiosteal haemorrhages.

By the time purpura develops the gums of a scurvy patient are always loose, tender, swollen and easily bleed. It must be borne in mind that the characteristic changes in the gums are found only in patients who have not lost their teeth. Purpura in scurvy develops as a consequence of impaired collagen synthesis in the vascular wall in combination with quantitative platelet changes. The Konchalovsky-Rumpel-Leede phenomenon and the pinch sign are sharply positive in most cases. A reduced content of vitamin C in plasma is a sign verifying the association of purpura with scurvy.

Degeneration of collagen fibres in the wall of the small vessels is evidently the cause of purpura senilis which is sometimes encountered not only among the aged, but in patients given steroid preparations for a long time. Intracutaneous extravasations with a diameter of 0.5 to 4.0 cm appear on the back, dorsal surface of the

hands, extensor surface of the forearms, and the bridge of the nose. Their dark red colour disappears in a few days, leaving a brown pigmentation.

Purpura is encountered in many **infectious diseases.** Signs of thrombocytopenia with characteristically prolonged bleeding time and impaired blood clot retraction predominate in the clinical picture of these diseases in some cases (e.g. in virus infections) and signs of haemorrhagic vasculitis in others (e.g. in endocarditis lenta). Simultaneous affection of both parts of the primary haemostatic mechanism is also often found (e.g. in meningococcal, pneumococcal or streptococcal sepsis).

Some congenital connective-tissue diseases are often complicated by haemorrhages which are believed to be a consequence of congenital defects in collagen synthesis in the walls of the small vessels. Qualitative deficiency of blood platelets is an inconstant sign of these diseases and evidently does not play a decisive role in the occurrence of haemorrhages. Congenital telangiectasia, osteogenesis imperfecta and the Ehlers-Danlos syndrome are considered to be typical representatives of this group.

Congenital haemorrhagic telangiectases (Rendu-Weber-Osler disease) are usually found on the mucous membrane of the tongue and nose, on the skin of the face, fingers and forearms, and less frequently, on the skin of the trunk and lower limbs. Sometimes they are detected on the mucous membranes of the pharynx, larynx, trachea, bronchi, oesophagus, stomach and other organs. They form arteriovenous anastomoses in the lungs.

Telangiectasia is at first red and disappears when pressure is exerted on the centre. It transforms later into a vascular spider which turns with time into a dark red or violet nodule elevated 1 or 2 mm above the surrounding skin or mucous membrane. Telangiectasia becomes invisible after bleeding. Any telangiectasia may bleed and be the cause of more or less marked anaemia. Bleeding from telangiectases of the nose and skin is most common, although bleeding from the internal organs is also encountered.

The diagnosis of congenital haemorrhagic telangiectasia may be suspected in a patient with recurrent (!) haemorrhages from the same organ. The diagnosis is confirmed by the discovery of telangiectases on the patient's skin or mucous membranes and the existence of similar ('monosymptomatic') bleedings in his relatives. Modern endoscopic methods of examination reveal telangiectases on the mucous membranes of the upper respiratory tract and the gastro-intestinal tract. The diagnosis of pulmonary telangiectasia coincides with the diagnosis of congenital pulmonary arteriovenous anastomoses. The mechanisms of haemostasis in intact vessels in patients with congenital haemorrhagic telangiectasia are not impaired. The bleeding time, blood platelet count, pinch sign, Kon-

chalovsky-Rumpel-Leede's phenomenon, blood clotting time, and blood clot retraction are normal.

Nasal, pulmonary, intestinal and subconjunctival haemorrhages and haematomas sometimes complicate the course of osteogenesis imperfecta whose main diagnostic signs are pathological fragility of bones, blue scleras, and otosclerosis. The formation of ecchimoses apparently without cause, haematuria, bleeding from the nose and gums, menorrhagia, and melaena are often encountered in the Ehlers-Danlos syndrome, a rare congenital disease whose main diagnostic sign is hyperpigmented skin on the shins, elbows and knees. Recurrent haemorrhages from any organ may be encountered in pseudoxanthoma elastica, a disease consequent upon congenital deficiency of the elastic membrane of the small vessels.

Platelet deficiency is manifested either by impairment of their thromboplastic function (thrombopathy) or by disturbed clot retraction (thromboasthenia). Both defects are sometimes discovered in the same patient. Although bleeding time is always above normal in both syndromes, the number of blood platelets is normal or even increased. The blood coagulation mechanisms are normal. Purpura in functional deficiency on the platelets is moderate and mainly manifested by haemorrhages from the mucous membranes (nasal bleedings, menorrhagia), easy formation of bruises, and prolonged haemorrhages after surgical operations.

Thrombopathy is often encountered in scurvy, uraemia, systemic lupus erythematosus, myeloproliferative diseases (polycythaemia, myelosclerosis), cirrhosis of the liver, diseases characterized by macroglobulinaemia, and in some other congenital and acquired diseases. Thromboasthenia (Glanzmann's disease) is a rare congenital disease. Its clinical manifestations are indistinguishable from the manifestations of thrombocytopathy.

For many years purpura may be the principal or the only syndrome of many **autoimmune diseases** (systemic lupus erythematosus, rheumatoid arthritis, haemolytic anaemia), **tumours of the lymphoid tissue** (multiple myeloma, lymphoid leucosis, lymphosarcoma, Waldenström's macroglobulinaemia) and some diseases of unknown origin, namely, **amyloidosis** and **essential cryoglobulinaemia.**

Waldenström was the first to study the causes of this purpura. In 1943 he reported the results of observations over patients with hyperglobulinaemia who, after long-term cooling, developed subfebrile temperature, oedema of the shins, and pain in the knees and ankles to which purpura appeared in attendance later. Petechiae and small ecchimoses (up to 2 mm in diameter) appeared on the skin of the shins every month and disappeared in one or two weeks. Recurrent eruptions covered both lower limbs entirely and pigmentation remained after their disappearance. Bleeding time was normal in all of them, while the Konchalovsky-Rumpel-Leede phenom-

enon was positive in most patients. The mechanisms of plasma protein coagulation did not change noticeably, although mild thrombocytopenia was found in some patients.

Immunoglobulins of different classes are always contained in the plasma of a healthy person. They are synthesized by the plasma cells of the bone marrow, spleen and lymph nodes. Increased content of monoclonic macroglobulins in blood is encountered in Waldenström's macroglobulinaemia. This disease is encountered mostly among the elderly. It is often complicated by cryoglobulinaemia the signs of which are considered to be persistent haemorrhages from the nose and gums whose mucous membrane resembles a loose bleeding sponge. Haemorrhages into the gastro-intestinal tract, under the retina, into the central nervous system, and into the skin and subcutaneous tissue (petechiae, ecchimoses) are often observed.

Cryoglobulins are plasma proteins capable of producing a precipitate on cooling. Besides haemablastoses, autoaggressive diseases (systemic lupus erythematosus, etc.) are the most frequent causes of the appearance of cryoglobulins in the blood. Under the effect of cooling cryoglobulins become jelly-like and even precipitate. Depending on the cryoglobulin concentration this may lead to increased blood viscosity or total arrest of circulation in the small vessels. The characteristic skin signs of the disease usually develop after the cooled part of the body is warmed. Cyanosis develops first and is replaced by erythema or urticaria. Petechiae, ecchimoses and vesicles with a haemorrhagic exudate appear later. The skin lesions (which may ulcerate) are attended by haemorrhages from the mucous membranes of the nose and gastro-intestinal tract. The frequent combination of cryoglobulinaemia with glomerulonephritis is associated with disturbed microcirculation and vasculitides, the underlying factor of which is the deposition of immune complexes into the wall of the small vessels. Cryoglobulins appear in the blood temporarily in infectious mononucleosis, endocarditis lenta, syphilis, acute nephritis, chronic hepatitis, idiopathic thrombocytopenic purpura, and some other diseases. The role of cryoglobulins in the development of visceral affections in these diseases is not known.

Short-term or long-term consistently progressive purpura is encountered in many diseases. Its clinical course is distinguished by great variability. Careful study of the causes of its development is one of the conditions of early diagnosis of many autoimmune diseases as well as of diseases of the blood, haematopoietic organs and lymph nodes.

Supplement XXV-1

The Most Common Causes of Purpura

1. Idiopathic thrombocytopenic purpura (Werlhof's disease).
2. Non-thrombocytopenic purpura.
3. Anatomical bone marrow lesion.
   Leukaemias.
   Metastases of carcinoma and haematosarcoma.
4. Toxic effects on the bone marrow.
   Drugs.
   Azotaemia.

Supplement XXV-2

Causes of Thrombocytopenia

1. Deficient thrombocytopoiesis.
   Myeloid metaplasia of the bone marrow.
   Tumours of the bone marrow.
   Metastasis of tumours to the bone marrow.
   Radioactive irradiation of the bone marrow.
   Toxic effect of drugs.
   Hypoplastic anaemia.
2. Accelerated destruction of blood platelets of immune genesis.
   Autoaggressive diseases.
   Thrombocytopenic purpura (Werlhof's disease).
   Purpura neonatorum.
   Drug-induced purpura.
   Immune thrombocytolysis in lymphoid leucosis, toxicosis of pregnancy, and after blood transfusion.
3. Platelet sequestration.
   Hypersplenism.
   Congenital haemangiomatosis.
   Extracorporeal circulation.
4. Other causes.
   Utilization coagulopathy.

Supplement XXV-3

Drugs which Often Induce Thrombocytopenic Purpura

Antimetabolites.
Aminazine (chlorpromazine hydrochloride).
Aminopyrine.
Acetylsalicylic acid.
Bucarban (carbutamide).
Butadione (phenyl butazone).
Butamide (tolbutamide).
Chlorpropamide.

Diacarb (fonurit).
Digitoxin.
Digoxin.
Diphenyl.
Erythromycin.
Hydroxychloroquin (plaquenil).
Hypothiazide (hydrochlorothiazide).
Isoniazide.
Laevomycetin (chloramphenicol).
Metylthiouracil.
Penicillin.
Phenacetin (acetophenetidin).
Phenobarbital (luminal).
Promedol (trimeperidine hydrochloride).
Quinidine.
Quinine.
Streptomycin.
Sulphazine (sulphadiazine).
Sulphalen.
Tetracycline.

Supplement XXV-4

Causes of Non-thrombocytopenic Purpura

1. Affection of vessels (vascular purpura).
   - Purpura simplex.
   - Allergic affection of vessels.
   - Haemorrhagic vasculitis of the Schoenlein-Henoch type.
   - Drug-induced purpura.
   - Autosensitization by red cells.
   - Scurvy.
   - Purpura senilis.
   - Bacteraemia and viraemia.
   - Congenital deficiency of vessels (genetic purpura).
2. Functional platelet deficiency.
   - Congenital thromboasthenia.
   - Moschcowitz's disease.
3. Other causes.
   - Macroglobulinaemia.
   - Cryoglobulinaemia.

Chapter XXVI

Transient Loss of Consciousness

Clear consciousness is a function of the cerebral cortex whose activity is maintained by a specific activating system located in the reticular formation of the brain stem (the diencephalic region, midbrain and the pons). The normal function of these regions of the brain is impaired in many diseases and injuries. Total or partial loss of consciousness occurs particularly often in diseases of the cardiovascular system.

The brain differs from other organs in that its metabolic activity is always maintained at about the same level. Besides, cerebral metabolism is almost completely aerobic. No measurable reserves of oxygen, glucose or other substrates necessary for metabolism are found in the brain cells. As a result, even short-term changes in the blood flow are attended by sharp disorders of cerebral functions.

A normally functioning brain consumes about 3.3 ml of oxygen per 100 g of matter every minute. A fall in the rate of oxygen consumption by 20-30 per cent is attended by disturbance of cerebral function. Loss of consciousness occurs when oxygen consumption falls below 2 ml/100 g/min. The degree of cerebral functional disorders is determined by the rate of the fall in oxygen consumption. Owing to the plasticity of the functions of the central nervous system, slowly developing ischaemia of the brain is compensated for a more or less considerable length of time by intensified extraction of oxygen from circulation.

Inadequacy of the compensatory processes is one of the causes of severe disorders of brain functions developing in its acute ischaemia.

Deficient blood supply to the brain is only one of the causes of its anoxia. Another no less important cause is hypoxaemia which always occurs in anaemias and with a drop in the barometric pressure of oxygen in the atmosphere. Anoxia of the brain often occurs under the effect of substances capable of forming poorly dissociating compounds with haemoglobin (e.g. carboxyhaemoglobin, sulphhaemoglobin) or of disturbing the normal course of oxidation processes in the cerebral tissue.

The cerebral vessels are functionally end vessels. Many authors deny the ability of these vessels to alter their lumen actively, but they all acknowledge the existence of autonomous regulation of cerebral blood flow and the dependence of its volume on the arterial pressure level.

Blood supply to the brain is normal till the mean arterial pressure gradually decreases to below 60 mm Hg. The fall of arterial pressure below this critical level is attended by a decrease in the cerebral blood flow. In a sharp drop in arterial pressure, the flow of blood in the brain decreases sharply even when the mean arterial pressure had not reached the critical level. This is evidently explained by the lack of time necessary for the development of compensatory processes in the circulatory system. Diffuse cerebral ischaemia occurring in such cases is clinically manifested by loss of consciousness.

Throughout life the blood glucose content in a man is maintained at about the same level. An invariable concentration of glucose in blood is just as necessary for normal brain function as invariable oxygen pressure. The constancy of the internal medium of the body, which is one of the conditions for its existence, is impaired in many diseases of the internal organs and endocrine glands. Some of these diseases are complicated by short-term or protracted loss of consciousness which may occur even in normal blood supply to the brain.

The brain is highly sensitive to a low content of glucose in blood. Depending on the severity and duration of hypoglycaemia unconsciousness may last for a short or a long time and is reparable or irreparable. In this section we merely describe differential diagnosis of short-term loss of consciousness occurring in diseases of the internal organs.

Some primary diseases of the central nervous system are marked by periodic episodes of impaired consciousness. For the differential diagnosis of these diseases an attempt should always be made to clarify the correlation in time between the loss of consciousness and the onset of the episode. In some cases consciousness is lost at the onset of the episode. It is believed that in such cases unconsciousness is a consequence of the stimulation of foci located in the reticular formation of the brain stem. In other cases the episode begins with signs of focal stimulation of the cerebral cortex while consciousness is still retained. In such instances unconsciousness develops some time after the onset of the episode. The duration of this period is determined by the time necessary for the stimulation from the cerebral cortex to be conducted to the deeply located layers of the reticular formation.

Loss of consciousness in head injuries may be a consequence of direct injury to the brain matter or a consequence of cerebral oedema attendant to the injury and leading to increased intracranial pressure and diffuse cerebral ischaemia. Both mechanisms are responsible for the loss of consciousness in contusion of the brain.

The practicing internist has to deal with transient loss of consciousness, for the main part, the underlying factor of which (Supplement XXVI-1) is acute circulatory failure associated with im-

pairment of some heart functions, with morphological changes in the vessels, and with deficient regulation of the vascular tonus, which may occur in diseases of the circulatory system itself and in diseases of other functional body systems.

Vasodepressor Syncope

Acute circulatory insufficiency in ordinary vasodepressor syncope begins with active dilatation of the peripheral vessels, mainly those of the muscles. The results of direct haemodynamic measurements allow the presumption that the rate of venous blood return to the heart and its minute volume do not change noticeably in this type of syncope. The principal haemodynamic effect consists in the inability of the body to raise the minute volume to meet the reduction of general peripheral resistance.

An ordinary vasodepressor syncope is the most common cause of temporary loss of consciousness. It occurs in most cases in males due to the effect of pain, small blood loss, fever or high environmental temperature. Much significance is attached to emotional factors, anxiety and fear in apprehension of some unpleasant unavoidable experience (e.g. taking of blood from the vein or trephination of a tooth cavity).

Unconsciousness does not occur instantaneously. It is often preceded by a short prodromal period during which the person experiences weakness, nausea, tinnitus, an urge to yawn continuously, a dimming of vision or dizziness; the pupils dilate, the skin turns pale, beads of perspiration appear primarily on the forehead and chin. The occurrence of these symptoms and signs is attributed to increased activity of the vegetative nervous system, to be more precise, with increased secretion of catecholamines and the antidiuretic hormone. The pulse in the prodromal period of syncope does not change or becomes somewhat faster.

With the gradual intensification of the reaction, muscular weakness increases, vision dims and the patient loses the sense of balance and faints. If the spell of unconsciousness lasts just a few seconds, the patient stays immobile, but if it lasts longer than 15 or 20 seconds, tonic and clonic convulsions appear and sometimes incontinence of urine.

Unconsciousness is always marked by the appearance of slow waves on the EEG, sinus bradycardia, sometimes by occasional extrasystoles and delayed atrioventricular conduction. The systolic arterial pressure usually falls to 55 to 60 mm, and the mean arterial pressure to 25 mm Hg. The skin is pale and cold. The conjunctival reflexes are often absent. Arterial pressure usually rises

as soon as the patient is in a horizontal position. In rare cases hypotension lasts several minutes or even hours.

Pallor, nausea, weakness and increased perspiration usually last during the entire period of hypotension. The entirety of these symptoms and signs is generally designated a syncope reaction.

A syncope reaction without loss of consciousness may sometimes be encountered in donors who are in a horizontal position before the blood is taken. The reflex origin of the syncope reaction in such cases is convincingly verified by clinical cases in which it developed before the skin was punctured or immediately after the puncture but prior to the collection of blood from the vein.

General weakness, skin pallor, perspiration and vomiting persist for some time after the syncope ends. The patient's attempt to sit up at this moment may cause another fall in arterial pressure with the appearance of all the symptoms and signs of syncope which had just vanished, including the characteristic EEG changes. After the syncope the skin is always moist and warm because the small vessels are dilated.

The diagnostic criteria of ordinary vasodepressor syncope are: the precursor period, bradycardia and hypotension during the period of unconsciousness, and a warm moist skin after recovery from syncope. If it proves possible to record the EEG during syncope, slow high-amplitude waves are demonstrated on it. The slow waves are replaced by a normal alpha rhythm as soon as the patient regains consciousness.

Postural Hypotension

The term postural or orthostatic hypotension designates clinical forms of short-term loss of consciousness when a person changes from a horizontal to a vertical position or when he stays erect for a long time.

When a healthy person gets up after lying peacefully in bed, his arterial pressure decreases slightly at first, but a few seconds later it returns to the initial level and sometimes even exceeds it a little. The initial fall in arterial pressure is explained by the displacement of blood towards the lower limbs due to the force of gravity.

The fall in arterial pressure leads to activation of the mechanical receptors embedded in the arch of the aorta and the carotid sinuses. Vasoconstriction begins when these receptors are activated and it counteracts the accumulation of blood in the veins of the systemic circulation. The mechanism of this adaptation reaction leads to an increase in the venous flow and minute volume of the

heart as a result of which arterial pressure returns to the initial level.

In postural hypotension, the mechanism of this adaptation reaction is inactive or insufficiently effective. The initial fall in arterial pressure when these patients get up from bed is not attended by adaptation vasoconstriction. As a result, blood accumulates in the veins of the systemic circulation. The venous return to the heart decreases and brings about a decrease in the minute volume and a more or less sharp reduction of arterial pressure. Blood supply to the brain proves inadequate when the mean arterial pressure falls below 25 mm Hg. The low adaptation vasoconstriction is explained by affection of the sympathetic part of the vegetative nervous system. Postural hypotension may be caused by discontinuation of the function of the peripheral parts of the sympathetic nervous system, i.e. those which are located in the spinal cord and the medulla oblongata or in the hypothalamus.

The clinical picture of unconsciousness in postural hypotension is stereotypical. Syncope always occurs under identical conditions which are usually well-known by the patient. When he is lying down, his arterial pressure is normal. Loss of consciousness usually occurs in the morning or at night immediately on getting up. In distinction from vasodepressor syncope, in postural hypotension the patient loses consciousness instantaneously with no precursor period. As soon as he takes a horizontal position, arterial pressure returns to normal and consciousness is regained.

The significance of postural blood sequestration for the occurrence of a state of unconsciousness is convincingly demonstrated by the test with blood substitutes. The arterial pressure of a patient with postural hypotension remains normal if albumin or some other blood substitute is quickly infused into the vein when he gets up. Hypotension in these patients is a consequence of disorders of neurohumoral mechanisms which ensure the constancy of arterial pressure.

Postural hypotension is usually encountered in diseases of the central or peripheral nervous system, in diabetes mellitus, alcoholism, and porphyria. It often develops in diseases of the spinal cord (transverse myelitis, syringomyelia, tabes dorsalis), medulla oblongata and hypothalamus. The vegetative nervous system is very often affected in these patients.

Diminished postural vasomotor reflexes are usually combined with impotence and disturbed activity of the sweat glands and gastrointestinal tract. Patients suffer particularly often from constipation, diarrhoea and reduced perspiration usually of one of the body areas.

The tendency of a patient to develop postural hypotension may also be revealed by functional tests, the most reliable of which are

those for the reaction of the cardiovascular system to the change to an erect posture and a rise in intrathoracic pressure.

The rapid change of a healthy person to an erect position is attended not only by the arterial pressure fluctuations described above, but by the appearance of tachycardia, increase in the concentration of aldosterone and catecholamines in blood, and an increase in their excretion in the urine. Neither tachycardia, increased concentration of aldosterone and catecholamines in blood nor their excessive excretion in the urine are recorded in a patient with orthostatic hypotension.

An increase in intrathoracic pressure (e.g. in Valsalva's manoeuvre) in a healthy person is attended by a mild transient reduction in arterial pressure. After the manoeuvre ends, the arterial pressure rises to a level slightly above the initial value. In a patient with orthostatic hypotension, Valsalva's manoeuvre causes a marked fall in arterial pressure which, after the manoeuvre ceases, gradually returns to the initial level, but never exceeds it.

Postural hypotension with spells of dizziness and unconsciousness is sometimes the only manifestation of a disease known as **idiopathic orthostatic hypotension.** When a patient with this condition changes quickly to a vertical position, no adequate increase in the tonus of the sympathetic nervous system occurs: the venous tonus does not increase, the arterioles are insufficiently constricted and there is no noticeable change in the blood epinephrine and norepinephrine content. Impotence and impaired perspiration usually in one body area may develop in attendance to these signs of the disease. Signs of involvement of the basal cerebral ganglia and the corticobulbar and corticospinal tracts appear in some patients with time. This variant of idiopathic orthostatic hypotension is generally known as the **Shy-Drager syndrome.**

Patients with severe idiopathic orthostatic hypotension are bedridden because any attempt to change from a horizontal to an erect position results in loss of consciousness. Convulsions develop if, as in vasodepressor syncope, the patient is kept standing for a lengthy period of time.

Orthostatic hypotension with short-term loss of consciousness must be differentiated from vasodepressor syncope which is often encountered in severe anaemia, convalescence after infectious diseases and after the patient had been recumbent for a long time, e.g. in myocardial infarction and fractures of the pelvic and femoral bones. The development of hypotension in these patients is attended by symptoms and signs of the syncope reaction described above. When the general condition of these patients improves, the spells of syncope disappear.

Loss of consciousness in orthostatic hypotension is not attended by signs of stimulation of the vegetative nervous system. They

occur every time the patient changes quickly from a recumbent to an erect posture irrespective of changes in his general condition. Arterial pressure drops sharply in a patient with orthostatic hypotension in the period of convalescence and after recovery from an infectious disease, both during anaemia and after its disappearance.

The regularity in the course of the disease is now mostly observed in patients with **iatrogenic orthostatic hypotension.** Orthostatic hypotension developing in patients subjected to bilateral sympathectomy is the simplest model of this condition. At one time, this operation was widely used in the treatment of malignant hypertensive disease and malignant hypertensive syndrome. Currently it is sometimes performed in the management of endarteritis obliterans of the lower limbs.

Arterial hypotension develops in these patients not when they are sitting in an armchair or lying in bed, but only when they quickly change from a recumbent to an erect position. Acute hypotension of a sufficient degree may cause loss of consciousness.

Orthostatic hypotension is often induced by a peculiar pharmacological desympathization of the body which is produced by exerting an effect on the principal vasomotor tonus or on catecholamine metabolism. The modern clinic uses such agents widely in treating hypertensive disease, angina pectoris and heart failure. Some of them act within some one organ, while others effect the functional condition of many systems and organs. Proceeding from purely practical considerations, we find it expedient to distinguish among these agents monoamine oxidase inhibitors, beta-adrenergic receptor blocking agents, hypotensive agents and diuretics.

Orthostatic hypotension is mostly encountered in treatment of arterial hypertension with guanethidine (Ismelin, Isobarin, Octadin) and other agents capable of blocking the activity of the postganglionic adrenergic nerves (Erina, 1973). Accumulating in the body, these drugs block the alpha and beta receptors of the sympathetic nerves and inhibit the property of the effective organs to respond to sympathetic stimulation. The developing desympathization of the vessels prevents the possibility of a change in their capacity when the patient changes to an erect position.

On entering the cholinergic ganglia of the vegetative nervous system the ganglion-blocking agents (Hexamethonium, Pentamine, Ganglerone, Pirilenum, etc.) assume a competitive relationship with acetylcholine and thus hinder or arrest the conduction of the nerve impulse from the pre- to the postganglionic fibres. In hypertensive disease and endarteritis, the conduction of nerve impulses to the sympathetic ganglia are disturbed first. As a result the tonus of the peripheral vessels diminishes.

The hypotensive effect of *Rauwolfia* preparations (Reserpine, Raunatin, Serpasil, Gendon, and others) is explained by their in-

hibitive action mainly on catecholamine and serotonin synthesis in the central nervous system. They reduce the reserves of catecholamines in the vascular wall to such a degree that stimulation of the sympathetic nerves fails to induce its contraction.

Preparations of alpha-methyldopa (Dopegyt, Aldomet, Presinol, etc.) react with the enzyme dopa-decarboxylase and disturb the formation of dopamine and, consequently, of epinephrine and norepinephrine. Hypotension induced by alpha-methyldopa preparations is a consequence of diminution of vascular tonus due to reduced reactivity of the vasomotor centre.

Apressin (Nepressin, Depressan, hydrazinophthalazine, and others) produces a hypotensive effect through primary inhibition of the myogenic vasomotor tonus, whereas diuretics reduce the principal vasomotor tonus in a secondary manner, via a decrease in the circulation volume and release of sodium ions from the vascular wall.

Monoamine oxidase whose inhibitors are prescribed in angina pectoris and depression also produce a noticeable effect on the tonus of the vascular wall. The use of these inhibitors is sometimes attended by a sharp fall in arterial pressure most likely due to block of the nerve impulses in the ganglia of the vegetative nervous system. Moreover, monoamine oxidase inhibitors drastically reduce the content of norepinephrine in the peripheral endings of the sympathetic nerves and thus suppress the capacity for vasoconstriction (Goodman and Gillman, 1960).

When the body is at full rest, agents blocking the beta receptors produce no noticeable effect on the cardiovascular system. They have a telling effect only during effort or emotional stress. Inderal, Isoprene and oxprenolol hydrochloride (Trasicor) block all beta receptors and prevent the catecholamine effect in the whole body. Practolol (Eraldin) possesses a selective effect. It blocks only the beta receptors of the heart. The vascular reaction to catecholamines does not change under the effect of Eraldin and orthostatic hypotension is therefore encountered less frequently after its use than after the use of other beta-blocking agents (Goodman and Gillman, 1960).

Some of the agents listed induce orthostatic hypotension in every patient, others only in some patients. Temporary loss of consciousness in patients given these agents is often mistaken for ordinary fainting fit. An erroneous diagnosis may be avoided if due consideration is paid to the following signs by which an ordinary syncope differs from orthostatic hypotension with loss of consciousness.

1. Orthostatic hypotension always occurs when the patient changes from a recumbent to an upright position. It often develops during physical exertion since these patients are incapable of responding to the exertion by an adequate increase in the vasomotor tonus because of functional desympathization. An ordinary syncope usual-

ly occurs when the patient is in an erect position, but not necessarily when he is getting up. It may also occur when the patient is seated, e.g. when watching a long TV show. Ordinary syncope may even occur when a person is recumbent, e.g. in donors whose blood is being collected from the vein for the first time.

2. A syncope reaction to a repeated identical situation (e.g. taking blood from the vein) becomes less and less manifested. With the increased incidence of such situations the reaction no longer occurs as a rule. The degree of orthostatic hypotension in repeated reproduction of the same conditions stays almost unaltered. If a patient given a large dose of guanethidine rises quickly from bed, his arterial pressure always falls to a level determined by the degree of desympathization and not by the number of times the patient gets up. Patients with orthostatic hypotension are usually well aware of the conditions under which they are bound to lose consciousness again. This is not true of patients who had suffered from ordinary syncope.

3. Ordinary syncope occurs in a patient with signs of hyperstimulation of the vegetative nervous system described above. In orthostatic hypotension loss of consciousness always occurs suddenly with no preceding prodromal period.

4. Bradycardia is a diagnostic sign of ordinary syncope. It is not encountered in orthostatic hypotension.

5. A sensation of warmth throughout the body and a warm, usually moist and sometimes even hyperaemic skin are encountered only in patients who had suffered from ordinary syncope. Signs of increased blood filling of the skin vessels are not observed after a fit of unconsciousness in orthostatic hypotension.

6. Convulsions may be encountered both in ordinary syncope and in orthostatic hypotension. Their occurrence in these two clinical entities is determined by the duration of the period of unconsciousness.

7. No signs of increased tonus of the sympathetic nervous system are encountered in patients with orthostatic hypertension during the period of unconsciousness or in the intervals between such episodes. Ordinary syncope is always marked by signs of increased tonus of the sympathetic and parasympathetic nervous system.

Acute Diminution of the Circulation Volume

A rapid decrease in the volume of circulating blood is often the cause of temporary loss of consciousness. The simplest and most illustrative form of this type of unconsciousness is encountered in

patients with sharply manifested varicose veins of the lower limbs. When these patients get up quickly, blood flows from the vena cava inferior by force of gravity and is pooled in the lower limb veins. The venous return to the heart reduces, and this causes an acute decrease in the minute volume as a result of which diffuse ischaemia of the brain develops. The diagnosis of this type of transient loss of consciousness is relatively easy and can usually be made immediately after questioning and examining the patient.

A sudden decrease in the blood flow to the heart underlies transient loss of consciousness in rare cases in the last trimester of pregnancy. When the expectant mother assumes a recumbent position, the enlarged uterus compresses the vena cava inferior or its large branches. As a consequence, the venous return and the minute volume fall sharply. When the pregnant woman gets up, the enlarged uterus descends into the pelvis, the vena cava inferior is no longer compressed, and normal conditions are restored for circulation in the body. Thus, the loss of consciousness in such cases occurs not after the woman gets up, but after she takes a recumbent position.

This type of unconsciousness is known in the literature as paradoxical syncope, because it occurs under conditions contrary to those of the loss of consciousness in ordinary syncope or in orthostatic hypotension. Similar mechanisms may cause loss of consciousness in pedicle tumours located in the abdominal cavity.

Rapid removal of great quantities of fluid from the abdominal cavity or from the urinary bladder is sometimes attended by transient loss of consciousness. The abdominal and pelvic veins in such cases are suddenly relieved from external compression. Their acute dilatation leads to the accumulation of a considerable volume of blood in the abdominal and pelvic cavities. The rate of venous return to the heart decreases as a result of which the minute volume falls sharply. A recumbent position of the patient is the best therapeutic and preventive measure counteracting loss of consciousness when large quantities of ascitic fluid are evacuated and large amounts of urine are removed from the bladder.

Elderly patients sometimes lose consciousness during micturition or soon after it. This usually occurs at night on getting up from bed. Without denying the role of the mechanical factor, we would like to draw attention to the role of other factors, particularly to orthostatic hypotension whose development is facilitated by reduction of the circulating blood volume at night, and to the increase of intrathoracic pressure developing during straining. The relative importance of each of these factors has not been studied because of the sudden occurrence and transient character of these conditions.

Diuretics are applied in modern medicine for treating disorders of water-electrolyte metabolism and for the management of arterial hypertension. Some patients are hypersensitive to these agents.

Even after the commonly prescribed doses are taken, diuresis in these patients increases so sharply that there is a hazard of their dehydration. In less manifested diuresis the volume of circulating blood also reduces considerably as a consequence of which a quick change from a recumbent to an upright position may be attended by a reduced venous return to the heart and hypotension. Loss of consciousness in treatment with diuretics alone occurs rarely. Hypotension in orthostasis is particularly sharply manifested when diuretics are combined with hypotensive agents.

Pleural Shock

Removal of a large quantity of effusion from the pleural cavity or the production of artificial pneumothorax is sometimes attended by loss of consciousness. In some cases it occurred during introduction of the air and was attributed to air embolism of the pulmonary veins and the resulting block of blood flow to the left ventricle. Without denying the possibility of this mechanism, it should nonetheless be borne in mind that in rare cases loss of consciousness occurred in response to the simple insertion of the needle, i.e. before the introduction of the air was begun.

Loss of consciousness in such cases (generally designated 'pleural shock') occurred in response to stimulation of the parietal pleura, i.e. developed according to the mechanisms of a vasodepressor syncope, rather than as a consequence of air embolism. The simultaneous effect of both mechanisms is possible in some cases of pleural shock. The relative significance of each may differ from case to case; that is why we decided to describe pleural shock as a clinical entity differing both from vasodepressor syncope and from postural hypotension.

Mechanical Obstructions of the Blood Flow

Sudden loss of consciousness associated with a change in the position of the body is one of the characteristic signs of heart diseases in which freely moving structures are present in its cavities. Mitral stenosis with a spherical thrombus in the left atrium and myxoma of the heart are the most common diseases. Freely moving thrombi in the heart cavities are extremely rare in endocarditis lenta and sarcoma of the heart.

A large spherical thrombus in the left atrium may obstruct the left atrioventricular orifice and cause partial or total arrest of the

blood flow from the atrium into the ventricle. Cerebral ischaemia develops with loss of consciousness or sometimes ends in death of the patient. Obstruction or drastic stenosis of the mitral orifice may recur, each time being marked by a stereotyped clinical picture which makes the diagnosis of this complication easier.

The episode usually occurs when the patient changes from a recumbent to an erect position. He suddenly develops dyspnoea and cyanosis which is particularly manifest on the skin of the upper trunk. The oral mucosa and the nose and ears are especially cyanotic. Micromacular cyanosis appears on the neck and chest. The radial pulse is usually not palpated while the pulse on the carotids is frequent and hardly felt. The patient becomes disoriented and loses consciousness.

The patient's condition improves when he takes a recumbent position or Trendelenburg's posture. Some of our patients preferred standing on their knees with the upper part of the trunk inclined forward. The diagnosis of loss of consciousness caused by spherical thrombus of the atrium is made only in patients with mitral stenosis. Besides, all our patients with this type of loss of consciousness had cardiac fibrillation.

Sudden loss of consciousness is also encountered in primary tumours of the heart, mostly in **myxoma,** which is localized in the left atrium in approximately 70 per cent of cases and in the right atrium in 25 per cent of cases. It usually grows on a pedicle. When the body is in upright position, the tumour descends to the atrioventricular orifice and narrows it noticeably. Cases have been described in which part of the tumour entered the left ventricle through the atrioventricular orifice with each contraction of the heart.

Sudden death in this disease is explained by block either of the atrioventricular orifice or of the orifices of the pulmonary veins. Death may also be caused by embolism of the cerebral vessels by tumour fragments.

Patients with atrial myxoma become unconscious only when they are in an upright position. The episode is usually preceded by dyspnoea, cyanosis and tachycardia. The attack of paroxysmal dyspnoea ceases if the patient lies down at the right time. Patients with pedicle myxoma of the atrium prefer to lie in bed because the episode recurs if any attempt is made to sit up.

In the intervals between the episodes there are more or less intensive pains in the region of the heart, often subfebrile body temperature, signs of mitral or tricuspid disease and in far-advanced cases, signs of circulatory insufficiency.

Myxoma of the heart should be suspected if transient loss of consciousness occurs when the patient takes an upright position and is preceded by paroxysmal dyspnoea, cyanosis and tachycardia.

The presence of pain in the heart, which is often very intensive, and the absence of a history of rheumatism permit loss of consciousness in myxoma of the heart to be differentiated from that in mitral stenosis with a spherical thrombus in the left atrium. Other signs by means of which these two diseases can be differentiated are discussed in the chapter 'Heart Failure'.

Primary Diseases of the Nervous System

Epilepsy. Many diseases of the central nervous system are marked by transient loss of consciousness. Sudden loss of consciousness, sometimes with a subsequent convulsive seizure, is encountered particularly often in epilepsy, narcolepsy, contusion of the brain, hysteria and some other diseases. The clinical picture of such impaired consciousness resembles that of simple syncope in many respects. Even experienced clinicians are often inclined to assess transient loss of consciousness without convulsions as simple syncope. Korovin (1973), for instance, describes a patient who had episodes of an unconscious state and mild abnormalities on the EEG in the form of diffuse small-amplitude slow waves for seven years prior to the development of typical epilepsy. The author believes these recurrent episodes of loss of consciousness to be simply fainting fits only because the parents of the patient asserted that these episodes had not been attended by convulsions.

The cited case shows the immense diagnostic difficulties confronting the physician who has to identify the cause of the episodes of unconsciousness. To overcome these difficulties either personal observation over the patient during the episode or a more or less lengthy follow-up of the course of the disease is necessary.

Recurrent episodes of loss of consciousness are a part of the clinical picture of epilepsy. The internist has to deal mostly with grand or petit mal epilepsy. Sudden loss of consciousness during which convulsive movements are observed is the most characteristic sign of grand mal epilepsy. Cortical and subcortical seizures are distinguished according to the localization of the epileptic focus.

Seizures of cortical epilepsy usually begin with aura, which may be visual, auditory, taste, olfactory or sensory. Subcortical epilepsy is characterized by sudden occurrence of the seizure. The seizure begins with tonic convulsions which change to clonic. After the convulsive movements cease, a soporose state occurs, which resembles sleep. The skin is often of a purple or cyanotic shade during the seizure, but is never pale. Clear consciousness is regained

gradually and not immediately after the seizure. On regaining consciousness, the patient often complains of headache.

The term 'petit mal epilepsy' designates transient loss of consciousness in which the muscular tonus may be maintained or lost. Simple petit mal epilepsy is a disease of childhood. These seizures sometimes persist in adults and after maturation they occur suddenly. The patient loses consciousness for just a few seconds fixed in the posture he had been in when the attack occurred. The static muscular tonus is preserved. After the end of the seizure, the patient usually continues the interrupted conversation or whatever he had been doing.

It is characteristic of loss of consciousness in akinetic (paralytic) seizure that the patient falls all of a sudden, but he immediately gets up on his own and continues whatever he had been doing. Convulsions do not occur during this seizure, and it is therefore often mistaken for a simple fainting fit or orthostatic collapse. Akinetic seizures begin in childhood. They may also persist in adulthood.

Korovin (1973) designates this type of seizure but of a longer duration (up to one minute) by the term 'syncopal minor seizure'. It always occurs abruptly. If the patient happens to be in an upright position, he falls suddenly, often with considerable injuries and bruises. The heartbeat does not change noticeably during these seizures, arterial pressure is normal, and incontinence of urine is sometimes noted.

Complete loss of consciousness occurs at times in patients who suffer from attacks of focal cortical epilepsy. It is attributed to the spread of the excitation to the brain stem. Consciousness is rarely lost in psychomotor epilepsy. Disturbances of behaviour attendant to the seizure allow it to be differentiated from orthostatic collapse and simple syncope.

Episodes of transient loss of consciousness are very rare in the beginning of epilepsy and usually occur only at night when the patient is in bed. Later the seizures occur more frequently and not only at night, but also in the daytime. The more frequent the seizures, the more rapidly the characteristic changes of personality develop. The patient grows irritable, short-tempered, susceptible to sharp affective reactions. In conversation the patient is typically ill-natured, unctuous and takes a long time in coming to the point. Both at home and at work these patients are known to be very exact.

In many cases the diagnosis of epilepsy can be verified by the results of electroencephalography, particularly if it is combined with functional tests. Characteristic changes on the EEG are found in approximately 76 per cent of patients with subcortical epilepsy and are manifested in most cases by the appearance of a slow wave-peak complex. The appearance of outbreaks of slow waves, chaotic

peaks and high-amplitude waves is more typical of cortical epilepsy.

An epileptic seizure must be differentiated from other types of transient loss of consciousness and particularly often from simple (vasodepressor) syncope and from orthostatic collapse. Purposeful questioning of the patient and observation of the clinical picture of the seizure allow for a definite diagnostic conclusion to be made in most cases. Special methods of examination or a longer period of observation over the course of the disease have to be resorted to much less frequently for clarifying the diagnosis.

Epilepsy often begins from childhood. In some cases it develops some time after a craniocerebral injury or infection. The patient can give no explanation for the seizures which occur as if spontaneously. Vasodepressor syncope is always a reaction of the patient to some stress situation. The patient himself describes the unusual circumstances or the situation which agitated him prior to the seizure. Patients with orthostatic collapse are usually well aware of the conditions under which it occurs.

An epileptic seizure may develop during sleep. Orthostatic collapse may occur at night, but never when the patient is asleep. The same is true of vasodepressor syncope. Loss of consciousness, when the patient is in a recumbent position, is never a consequence of orthostatic collapse or syncope since they do not appear, but, on the contrary, disappear as soon as the patient changes to a recumbent position.

Detailed questioning about the sensations preceding loss of consciousness also often helps in detecting signs which are of differential diagnostic importance. Orthostatic collapse, subcortical epilepsy and akinetic and syncopal petit mal epilepsy usually have no precursors. Dimness of vision and excessive perspiration often appear before vasodepressor syncope. A seizure of cortical epilepsy is often preceded by tactile, visual or olfactory aura.

The skin and visible mucous membranes are strikingly pale during syncope and orthostatic collapse, while the muscles are atonic and arterial pressure drastically low. The skin is cyanotic in grand mal epilepsy but normal in colour in petit mal epilepsy. Euphoria is noted immediately after syncope and the skin is hot and moist. There are no vegetative disorders during a seizure of petit mal epilepsy. Euphoria, disorientation of the patient in his environment or even a twilight state are encountered for some time after seizure. The character of the convulsive reaction makes it possible to confidently distinguish syncope and orthostatic collapse from grand mal but not from petit mal epilepsy.

Bruises resulting from falling, and incontinence of urine, biting the tongue and glassy eyes were formerly considered to be reliable signs of epilepsy. It is currently known that they may also occur in severe syncope or in severe loss of consciousness of other origin.

The cause of transient loss of consciousness often becomes clear

after studying the typical features of the patient's personality. It should be pointed out, however, that if the disease had only begun recently the results of the study are not reliable. The results of electroencephalography considerably help in such cases, especially if they are carried out with the use of different activation methods. It should only be borne in mind that a normal EEG record does not rule out the diagnosis of epilepsy.

Repeated examination of the patient and a more or less lengthy period of observation over the evolution of the disease and the character of changes in the patient's personality must sometimes be resorted to in making the differential diagnosis between epilepsy, vasodepressor syncope, and orthostatic collapse.

Loss of consciousness is a regular occurrence in **contusions and concussions of the brain.** The case record usually permits this type of transient loss of consciousness to be easily distinguished from vasodepressor syncope and orthostatic collapse.

Short-term loss of consciousness is often encountered in transient and usually sharply manifest elevations of cerebrospinal fluid pressure in the ventricles of the brain. This occurs particularly often in tumours of the posterior cranial fossa (Bruns' syndrome) and much less frequently in hypertensive crises.

Obstruction of the aqueduct of Sylvius or Monro's foramen sometimes occurs in **tumours of the brain** and is marked by a sharp elevation in cerebrospinal fluid pressure. This is manifested clinically by an attack of severe headache which may be complicated by a sudden loss of consciousness and even by an epileptiform seizure. The presence of neurological symptoms indicating that the pathological process is localized in the posterior cranial fossa suggests a tumour of the brain. The final diagnosis is established by a neurologist.

Dizziness is often experienced immediately before loss of consciousness in patients with increased craniocerebral pressure. A brief spell of dizziness also often precedes loss of consciousness in orthostatic collapse, anaemia, increased activity of the carotid sinus, atherosclerosis of the cerebral arteries and in many other diseases. Dizziness in these patients must be differentiated from dizziness encountered in lesions of the vestibular apparatus. A patient with one of the above-listed diseases thinks that he is losing his balance. He may even fall but he never complains that objects seem to be swimming before his eyes in a certain plane, or that he falls or sways always to the same side. Dizziness of the types described is never attended by nystagmus and is not the main or the principal symptom of the disease.

Spells of dizziness in diseases of the vestibular apparatus are usually of a systemic character and predominate in the clinical picture of the disease. A patient with an attack of such dizziness often loses

his balance and always falls to the same side. The patient himself and the people around him regard these falls as breif fainting fits. Examination of the patients after the attack reveals impaired function of the vestibular apparatus (the labyrinth, vestibular nerve, vestibular nucleus or cerebellum). A more or less marked nystagmus is often found.

The function of the vestibular apparatus is particularly sharply disturbed in **Meniére's syndrome.** The attacks of dizziness in this syndrome may last from several minutes to several days. They are sometimes attended by tinnitus, vomiting, abdominal pain and diarrhoea. Angioneurotic oedema of the labyrinth is the underlying factor of this syndrome in most cases. The mechanisms of the loss of consciousness in lesions of the vestibular apparatus have still not been sufficiently studied.

Patients with **narcolepsy** do not lose consciousness during the spells of sleep characteristic of this disease and are easily awakened. We discuss narcolepsy here for purely practical considerations. The muscular tonus of a patient with narcolepsy is often lost during strong emotional excitation. In a fit of laughter or anger his knees suddenly give in and he falls to the ground. The patient himself and the people around him think this episode is a light and brief fainting fit. Detailed conversation with the patient reveals the true cause of the loss of the postural tonus.

The sense of body equilibrium in space is attained by the coordination of afferent impulses arising from the vestibular apparatus, visual analyser and peripheral locomotor apparatus. We perceive the loss of balance as vertigo. In disorders of the function of the visual analyser dizziness is combined with diplopia. In impaired function of the vestibular apparatus, vertigo is combined with the feeling that surrounding objects are swimming in one direction and that the body is falling always in one direction.

Intensive stimulation of the vestibular apparatus (oedema or ischaemia of the labyrinth, stimulation of the vestibular nerve, vestibular centre or cerebellum) is usually attended by marked vegetative reactions and disorders of the motor and secretory functions of the gastro-intestinal tract. Vomiting and diarrhoea, often developing in Meniére's syndrome, may serve as a clinical illustration of this. Loss of muscular tonus is another vegetative reaction to the stimulation of any component of the vestibular apparatus.

In such cases the patient falls not because of loss of consciousness and the episode must be differentiated from vasodepressor syncope and from temporal (psychomotor) epilepsy in which the patient loses his balance only after he becomes unconscious.

Vertigo may be the initial sign of epilepsy with the epileptic focus localized in the temporal lobes. Dizziness in such type of epileptic seizure is often combined with auditory and visual hallu-

cinations. Stimulation of the vestibular apparatus in such cases plays the role of one of the stimulators of pathological cerebral activity.

Diagnosis of the causes of dizziness occurring in combination with loss of consciousness cannot be based on the explanations given by the patient or people around him on the character of the fit. In order to identify these causes, a detailed study of the patient must be made with the use of different tests for the function of the vestibular apparatus and the condition of the central nervous system.

The internist is faced with the responsible task of objective evaluation of the adequacy of blood supply to the brain. To do this, it is necessary to exclude a possible association of dizziness and transient loss of consciousness with functional disorders of the heart and with deficient blood supply to the brain due to affection of arteries arising from the arch of the aorta.

Attack of hysteria usually develops only when there is an audience. It is a reaction of the patient to a conflicting situation. Witnesses of the attack believe it to be vasomotor syncope or an epileptic seizure. High significance in the differential diagnosis between these clinical entities is attached to studying the patient's personality and the peculiarities of his behaviour in the past and during the episode.

The specific features of hysterical behaviour (certain mannerism a wish to be the centre of attention) usually appear in adolescence and almost never appear for the first time after the age of thirty The diagnosis of hysterical syncope made for the first time in a middle-aged or elderly patient is risky, to say the least. If it can be made, then, at any rate only after organic diseases have been ruled out and only after it has been established that symptoms of hysteria had existed prior to the development of this attack.

Witnessing of the attack discloses a number of signs which are of high differential diagnostic significance and often permit hysteria to be differentiated from simple syncope.

Simple syncope is characterized by an acute course. Its menacing picture sets in suddenly and ends as soon as the patient assumes a recumbent position. An attack of hysteria is milder and of longer duration. It sometimes lasts tens of minutes. Although a patient with hysteria falls suddenly, his consciousness is only partially impaired. A change to a recumbent position characteristically does not lead to recovery from the syncope.

In simple syncope the skin is deathly white and the pulse slow Amnesia occurs at the end of syncope and the skin becomes sweaty and moist. A certain euphoria is often noted. In an attack of hysteria, the skin and visible mucous membranes either do not change in colour or become slightly cyanotic. Bradycardia is not noted

during the attack. Questioning reveals that the patient can recall at least some of the details of the attack. There is no euphoria after an attack of hysteria and the skin temperature is normal. Urine is often passed during a deep vasodepressor syncope. This is not characteristic of an attack of hysteria.

Much less frequently an attack of hysteria must be differentiated from an epileptic seizure. They differ mostly in the conditions of their origin. It is quite justified to call an attack of hysteria a situation attack. It is the patient's response to a definite situation and occurs only under certain circumstances in the presence of witnesses. It may take place at night but never during sleep. An epileptic seizure occurs with no apparent cause at any time of the day or night in no association with the attendant circumstances and often during sleep. An epileptic seizure begins with aura and a characteristic cry. After the patient falls (during which serious injuries may be sustained) tonic and then clonic convulsions develop, the tongue is bitten and urine is involuntarily passed. The pupils fail to react to light and the deep reflexes are inhibited. The skin is usually purplish red and cyanosis develops when breathing is impaired.

A patient who falls during an attack of hysteria usually does not sustain severe injuries. During the attack (which may continue for quite a long time) there is no alternation of tonic and clonic convulsions characteristic of epilepsy, the patient does not bite his tongue and urination is under control. Instead of the characteristic initiating cry, biting of the lips, cries and moans occur during the attack. The pupils react to light and the tendon reflexes are normal.

No recollection of the attack, and sleep and confused consciousness after the attack are encountered only in epilepsy. Examination of the patient after the epileptic seizure discloses the changes in personality mentioned above and often reveals characteristic EEG abnormalities. Hysteria is marked by changes in the patient's behaviour which are different from those occurring in epilepsy. The EEG is normal in hysteria.

Increased Carotid Sinus Activity

The carotid sinus plays an important role in arterial pressure and heart beat regulation. It is localized at the bifurcation of the common carotid artery. The numerous nerve endings found here form Hering's sinus nerve whose fibres stretch to the vasomotor centre as components of the glossopharyngeal nerve. The effector limb of the reflex arc is a part of the vagus nerve. Compression of the carotid sinus causes vasodilatation and deceleration of the rate of cardiac contractions. Vasodilation is most manifest in the skin, muscles and abdominal organs.

Stimulation of the carotid sinus may cause the arterial pressure in a healthy person to drop by 10 to 40 mm Hg. The sensitivity of the carotid sinus mechanoreceptors is sometimes sharply increased, in which event its slight stimulation may be attended by a sharp fall of arterial pressure and bradycardia. This results in vertigo and sometimes in loss of consciousness, which may be transient or protracted. In the latter case convulsions develop. The totality of these symptoms and signs is designated the 'carotid sinus syndrome'.

The diagnosis of this syndrome may be established only if mechanical or some other stimulation of the carotid sinus reproduces all or almost all symptoms and signs occurring in the patient spontaneously. This syndrome is mostly encountered in elderly and aged individuals.

According to the character of haemodynamic disorders, **cardioinhibiting and depressor types of the carotid sinus syndrome** are distinguished. The cardioinhibiting type is mainly manifested by bradycardia which may develop to the point of a brief heart arrest. Neither bradycardia nor hypotension occur in patients with this type of the syndrome after preliminary prescription of atropine or sympathomimetic agents.

The depressor type of the syndrome is very rare. It is mostly a consequence of the dilatation of the peripheral vessels. Hypotension and bradycardia develop in this type despite preliminary medication with atropine. Study of many cases showed that both types of the syndrome may be encountered in the same patient. Diffuse cerebral ischaemia in these patients may be a consequence both of hypotension caused mainly by the dilatation of the peripheral vessels and of bradycardia.

The cardioinhibiting type of carotid syncope is mostly encountered in elderly and aged males. Questioning of the patient often brings to light that vertigo and sometimes loss of consciousness usually occur when the head is turned in a certain direction and the carotid sinus is simultaneously slightly compressed. The combination of such conditions occurs particularly often when shaving or when a tight-fitting collar is worn.

Transient loss of consciousness often develops due to the effect of visceral reflexes. Reflexes the afferent part of whose arcs is a component of the vagus nerve are of particular importance. Syncope arising from stretching of an oesophageal diverticulum is generally known. It occurs when swallowing food. Fits of such syncope cease after surgical removal of the diverticulum. Dizziness and syncope are encountered in patients given cardiac glycosides. They cease when the cardiac glycosides are discontinued or sympathomimetic agents are additionally prescribed.

A marked increase in the tonus of the parasympathetic nervous

system is probably one of the important causes of mild dizziness and transient loss of consciousness in patients with pulmonary hypertension and in those given agents which increase the tonus of the parasympathetic nervous system. Insulin also increases noticeably the sensitivity of the carotid sinus to reflex influences. Vertigo and syncope which are sometimes encountered during insulin therapy no longer appear after it is discontinued. Unfortunately, the cause of increased reflex activity of the carotid sinus remains unclarified in many instances. From the results of long-term follow-up of the same patients, it may only be stated that the activity of this reflex mechanism increases noticeably under the effect of fatigue, worry and anxiety. More or less lengthy periods of increased activity of the reflex are replaced by periods of normal activity.

Increased reflex activity of the carotid sinus should be suspected in transient loss of consciousness, particularly in elderly individuals with a clinical picture of coronary atherosclerosis or aortic stenosis and in patients taking cardiac glycosides or parasympathomimetic drugs. Hypotension, delayed heart beat, sometimes even to the point of a short-term total heart arrest, are characteristic diagnostic signs of the syndrome. The patient loses consciousness both in an upright and in a recumbent position.

The diagnosis of the carotid sinus syndrome may be substantially supported by the results of electrocardiography. The ECG changes in this syndrome have been studied well on patients examined during manipulations for producing this syndrome by exerting pressure on the carotid sinus. The ECG of these patients demonstrates sinus bradycardia and sometimes complete atrioventricular block with decelerated ventricular contractions to 20 and even to 10 per minute. In rare cases, complete cardiac arrest occurs or arrhythmias (multiple extrasystoles, ventricular tachycardia, ventricular fibrillation) develop.

The vasodepressor type of the carotid sinus syndrome is a very rare occurrence in its pure form. It differs from the cardioinhibiting type only in that it may occur even in patients given atropine before compression of the carotid sinus. A mixed type of the syndrome is diagnosed in cases in which the prescription of atropine prevents loss of consciousness, but cannot prevent the development of moderate hypotension.

In some cases, pressure exerted on the carotid sinus results in unconsciousness during which the heart beat does not change and there is no fall in arterial pressure. Loss of consciousness in such cases is most likely the consequence of reduced blood supply to the brain induced by this manipulation in patients with atherosclerosis of the carotid and cerebral arteries.

Temporary loss of consciousness in the carotid sinus syndrome must be usually differentiated from similar transient loss of con-

sciousness in vasodepressor syncope, the Adams-Stokes-Morgagni syndrome, and in stenosing atherosclerosis of the common carotid artery.

In most cases, the carotid sinus syndrome can be differentiated from these clinical entities if it is taken into account that vasodepressor syncope occurs only in patients who are in an upright position, whereas carotid syncope may also be encountered in recumbent patients. Pressure on the carotid sinus does not induce vasodepressor syncope and preliminary administration of atropine does not prevent its development.

The Adams-Stokes-Morgagni syndrome is encountered in complete atrioventricular block and when incomplete atrioventricular block transforms into a complete block. Consciousness may be lost when the sinus node is stimulated in patients with type II incomplete atrioventricular block. In all the cases listed, just as in the carotid sinus syndrome, loss of consciousness is caused by temporary asystolia. Electrocardiography in the periods free of attacks demonstrates a normal sinus rhythm in patients with the carotid sinus syndrome and disorders of conduction in the other conditions listed.

The Aortic Arch Syndrome

Stenosing atherosclerosis of the common carotid artery may cause insufficient blood supply to the brain. This insufficiency is at first manifested only during physical exertion or emotional stress. If one of the carotid arteries is obstructed, compression of the other will lead to diffuse ischaemia of the brain even when the patient is in a state of emotional and physical rest.

Loss of consciousness in such cases is not associated with the reflex activity of the carotid sinus. This is proved by the possibility of reproducing the clinical picture of syncope even after procaine hydrochloride anaesthesia of the carotid sinus receptors. In practice, the atropine test allows the carotid sinus syndrome to be distinguished in most cases from the aortic arch syndrome with impaired blood flow in the major vessels. Medication with atropine prior to stimulation of the carotid sinus has no effect on the blood flow in the carotid artery in obstructive lesions of the carotid artery and arteries of the head. Preliminary administration of atropine prevents syncope in most cases of the carotid sinus syndrome.

Bouts of vertigo and transient loss of consciousness are often encountered in the aortic arch syndrome, which, just as the carotid sinus syndrome, may be encountered in the middle-aged, elderly, and aged. The aortic arch syndrome in middle age is usually a complication of inflammation of the aorta and its branches. In the elderly and aged, its underlying factor is atherosclerosis of the aorta

and branches arising from its arch. The clinical picture of this syndrome is most severe in dissecting aneurysm of the aortic arch.

Syncope in dissecting aneurysm of the aortic arch is a consequence of cerebral ischaemia caused by stenosis of the orifices of the arteries arising from the arch. Stenosis of the brachiocephalic trunk and the left common carotid artery leads mainly to motor disorders. Syncope is not the leading sign of dissecting aneurysm of the aorta and its diagnostic signs are therefore not included in the further analysis in this chapter.

Stenosis of the carotid artery is of a generalized character as a rule. The common carotid artery, including the bifurcation, and sometimes also the internal carotid artery are usually affected. The stenosis is caused by compression of the arteries by a scar or tumour, and by arteritis and atherosclerosis. The left artery is stenosed more frequently than the right.

Stenosis or occlusion of the common carotid artery results in weakening or disappearance of its pulse on the neck. In compression of the carotid artery by a scar or tumour, the blood flow in it is reduced very slowly and when the patient applies to the doctor for the first time the artery still pulsates. The blood flow ceases or weakens sharply only if one of the arteries is clamped or sharply bent when the head is turned in certain ways.

Isolated affection of the carotid artery is rare. Simultaneous affection of other arteries arising from the aortic arch is usually encountered. Combined stenosis of the carotid and subclavian artery is particularly frequent.

Transient loss of consciousness in affection of these arteries is explained by ischaemia of the brain whose signs are detected most clearly in simultaneous affection of the vertebral arteries (branches of the subclavian artery). Loss of consciousness is rarely an isolated sign. It usually develops at the same time as vertigo (caused by ischaemia of the vestibular apparatus) and disorders of vision in the form of diplopia, dimness of vision, and temporary blindness.

The final diagnosis of stenosis of the carotid or subclavian artery is established after arteriography which shows the severity and length of the stenosis. Ophthalmodynamometry is of considerable diagnostic aid. Pressure in the central artery of the retina is always lower on the side where the carotid artery is occluded, than on the healthy side. In the carotid sinus syndrome, the carotid arteries are not obstructed and intraocular pressure is the same on both sides.

Heart Arrest and Arrhythmias

Heart diseases are the most frequent causes of loss of consciousness in elderly and aged individuals. Transient loss of consciousness caused by disorders of the heart rhythm is particularly frequent in myocardial infarction and other diseases prevalent among individuals of this age group.

Automaticity inherent in the sinus node may be inhibited under the influence of an inflammatory or some other morbid process. In aged persons it is often inhibited due to increased tonus of the vagus. When the sinus node loses its property of pacemaker this function is usually assumed by the atrioventricular node or the centres localized in the ventricle. If, for some reason, these centres are tardy or incapable of assuming the function of a pacemaker, diffuse ischaemia of the brain develops and terminates in loss of consciousness or sudden death from heart arrest.

Disorders of conduction through the atrioventricular node or the His bundle are complicated by fits of unconsciousness in about half the cases. Stokes (1846) was the first to provide a correct explanation of the causes of these episodes. His conclusions were based on the results of studying his own six cases and three cases from the practice of his teacher Adams (1827). This syndrome had been described even earlier by Morgagni (1769) and Gerbetius (1619).

Loss of consciousness in total or partial cardiac block is generally designated as the Adams-Stokes-Morgagni syndrome. Loss of consciousness in patients with signs of atrioventricular block, which is detected during the attacks and persists in the intervals between them, is now included in this syndrome. Spells of unconsciousness are often the first clinical manifestation of impaired atrioventricular conduction.

The causes of atrioventricular heart block are very numerous. They are listed in detail in the chapter 'Arrhythmias'. At this point it is important to note that any transient loss of consciousness in a patient given cardiac glycosides or anti-arrhythmic agents should be regarded before all else as a manifestation of the toxic effect of these drugs. Only after this possibility is ruled out may the syncope be attributed to arrhythmia itself. The previously generally accepted opinion that the Adams-Stokes-Morgagni syndrome is only encountered in acquired heart block proved to be inaccurate. Cases of congenital heart block with recurrent attacks of transient loss of consciousness have been recently described. These attacks were completely relieved only after implantation of an artificial pacemaker.

It was at first believed that short-term ventricular arrest caused loss of consciousness only in complete heart block. There is no longer

any doubt today that loss of consciousness clinically indistinguishable from the Adams-Stokes-Morgagni syndrome may occur in severe bradycardia and in all tachyarrhythmias complicated by marked diminution of the minute volume and flow of blood through the brain. This is encountered particularly often in ventricular tachycardia, atrial flutter and fibrillation, supraventricular paroxysmal tachycardia, and in some inheritable heart diseases (supravalvular form of aortic stenosis, hypertrophic cardiomyopathy in arrhythmias complicating the Wolff-Parkinson-White syndrome).

Loss of consciousness when one cardiac rhythm changes to another (i.e. when a normal rhythm changes to complete heart block or ventricular tachycardia) is a clinical reflection of the period of asystolia, which lasts until a new pacemaker (ventricular) begins functioning instead of the old one. Clinic convulsions appear when the duration of this 'pre-automatic pause' exceeds 20 to 25 seconds.

An attack of ventricular tachycardia is sometimes followed by a period of asystolia the duration of which is determined by the time required for the restoration of the sinus pacemaker automaticity whose excitability had been inhibited during tachycardia. Loss of consciousness in ventricular flutter is explained by the practically total cessation of ventricular function concerned with forcing blood into the arteries of the systemic and pulmonary circulation.

It was shown that loss of consciousness in the delayed repolarization syndrome is caused by transient attacks of ventricular fibrillation. Depending on the duration of the attack either pallor and dizziness develop or deep loss of consciousness with convulsions and incontinence of urine occurs. The attacks begin with palpitation and vertigo combined with intermissions in heart activity. Occasional extrasystoles are demonstrated on ECGs recorded after the attack.

Considerable prolongation of the *QT* interval on the ECG is a characteristic diagnostic sign. It is generally known that physical exertion is attended by an accelerated heart beat in a healthy person. The length of the *QT* interval decreases during tachycardia. Effort in patients with the delayed ventricular repolarization syndrome is attended by an increase in the rate of cardiac contractions but the *QT* interval does not diminish, but even becomes longer. The attacks of vertigo and loss of consciousness usually arise during alarm or fright. Increased length of the *QT* interval is the only sign of the syndrome in periods free of attacks. The disease is inherited and is encountered in several generations of the same families.

The clinical manifestations of cerebral ischaemia in arrhythmias and disorders of conduction vary from mild vertigo to complete loss of consciousness. In ischaemia of a longer duration clonic convulsions occur which are sometimes mistaken for an epileptic seizure. Loss of consciousness in disorders of rhythm occurs all of a sudden and consciousness is regained just as suddenly. Pallor of

the skin at the onset of the attack and the appearance of reactive hyperaemia of the face immediately after the attack ceases are characteristic signs. Depending on the initial position of the body the state of unconsciousness occurs in 7 to 17 seconds and the convulsive movements in 20 or 25 seconds after cardiac arrest.

Aura often precedes an epileptic seizure and its character is always the same. An epileptic seizure never ends instantaneously. The patient remains stuporous some time after the fit is over. Pallor and hyperaemia of the face are seen neither during the epileptic seizure nor after it. There are no sharp changes in the heart beat during an epileptic seizure.

Although it is attended by bradycardia, vasodepressor syncope begins with a presyncopal state which is never encountered in arrhythmic syncope. Euphoria develops after vasodepressor syncope ceases, but does not occur after arrhythmic syncope. Vasodepressor syncope mainly occurs when the patient is in an upright position. Loss of consciousness in arrhythmias and disorders of conduction may recur even in a bedridden patient.

The association of spells of unconsciousness with disorders of rhythm and conduction is finally established by recording the ECG continuously or during the spell. ECG recording in the periods between attacks is also of high diagnostic significance. In most cases, it demonstrates one of the types of conduction or rhythm disorders which are often complicated by spells of unconsciousness.

Pulmonary Hypertension

Changes in haemodynamics after an acute elevation of pressure in the pulmonary artery were studied in detail. It was found that stimulation of the mechanoreceptors of the pulmonary artery was attended by a change of reflex disorders in systemic circulation. The principal disorders were reduced pressure in the aorta and its branches, markedly diminished coronary blood flow, and storage of blood in the spleen.

The results of these experiments provide a basis for recognizing the principal importance of the reflex factor in the mechanisms of syncope in pulmonary hypertension.

Thrombosis of the right and left pulmonary arteries or more than half of all their small branches leads to the development of the clinical picture of severe collapse. Obstruction of the moderate calibre pulmonary branches usually results in infarction of the lung. Temporary loss of consciousness is often the first and sometimes the only sign of embolism of the small branches of the pulmonary artery. This complication is particularly frequent in elderly persons

compelled to keep to bed for a long time because of bone fractures, myocardial infarction or severe heart failure.

The sources of embolism in most patients with heart failure are the deep veins of the lower limbs; in patients with myocardial infarction intracardiac thrombi are the sources. The use of new, more precise methods of examination disclosed that embolisms of the small branches of the pulmonary artery occur much more frequently than they are diagnosed. They should be suspected in most cases of loss of consciousness in a patient with heart failure. This suspicion becomes all the more probable if the spells of unconsciousness recur as if in a series, following one another at small intervals of time.

Although embolism of a small branch of the pulmonary artery may be manifested merely by a short-term loss of consciousness, repeated examination of the patient reveals other signs of this complication in most cases: temporary intensification of dyspnoea or a single attack of nocturnal paroxysmal dyspnoea, elevation of body temperature sometimes only to subfebrile levels for one day, moderate leucocytosis and the appearance of small foci of deficient blood supply to the lungs on the scanogram or foci of peri-infarction pneumonia on the radiograph.

Transient loss of consciousness also occurs in primary and secondary pulmonary hypertension. It is mostly associated with physical effort. The underlying factor is acute increase of pressure in the pulmonary artery occurring mostly as a consequence of the incapacity of the left ventricle to transform the increased venous return to an adequate minute volume. This factor plays a major role in the origin of syncope in aortic stenosis, mitral insufficiency, mitral stenosis and atherosclerotic cardiosclerosis.

A decrease in the minute volume may also be a consequence of the inability of the right ventricle to overcome the abruptly increased resistance in pulmonary circulation. The action of this mechanism is easily discovered in pulmonary stenosis, pulmonary infarction, severe pneumosclerosis and other diseases.

A diminished minute volume is only one of the causes of cerebral ischaemia in acute pulmonary hypertension. Another cause is reduced arterial pressure in systemic circulation induced by the activity of the reflex mechanism which had been studied by V. V. Parin. The degree of this reflex is in turn determined by the carotid sinus receptor apparatus.

Thus, cerebral ischaemia which is the underlying factor of unconsciousness in pulmonary hypertension results from the interaction of several mechanisms. The importance of each may differ in some cases of syncope. The proper evaluation of each factor is vitally important in prognosticating the condition and in choosing the most effective therapeutic measures.

Syncope in whooping cough, laryngitis or bronchitis occurs during or at the end of a fit of coughing. This type of syncope was described for the first time by Charcot in 1876. Its developmental mechanisms were studied only after World War II. It was found that the fit of coughing was attended by an increase of intrathoracic pressure to 300 mm Hg. A simultaneous increase of cerebrospinal fluid pressure was noted.

Under the effect of high intrathoracic pressure, the blood return to the heart noticeably decreases and the minute volume diminishes, which aggravates the conditions for supplying blood to the brain. The high cerebrospinal pressure also hampers normal blood supply to the brain. In sufficient activity of these mechanisms diffuse cerebral ischaemia develops; it is manifested clinically by loss of consciousness. Syncope sometimes occurring in Valsalva's manoeuvre possesses the same mechanism. Any strong physical exertion when the larynx is closed may lead to the same result. Syncope of such origin is sometimes encountered among aged individuals suffering from constipation when they strain during defaecation.

Metabolic Disorders and Other Conditions

Transient loss of consciousness is often encountered in **congenital heart diseases** (tetralogy of Fallot, patent ductus arteriosus, atrial or ventricular septal defects). It occurs in young children when they cry and during muscular overstrain and emotional excitation in older children. The tachycardiac form of arrhythmia or sharp bradycardia may serve as the disclosing factor.

We had several female patients under observation with an atrial septal defect who had made no complaints over a considerable length of time and transient loss of consciousness during delivery was the first clinical manifestation of their disease. Physical effort in such patients is attended by abrupt increase of pressure in the pulmonary artery. As a consequence, large quantities of venous blood return to the systemic circulation. Acute hypoxaemia and ultimately diffuse anoxia of the brain develop. Loss of consciousness is its clinical manifestation.

Hyperventilation occurring spontaneously mostly under the effect of alarm, anxiety or any pain stimulation leads to syncope. A less frequent occurrence is voluntary hyperventilation which like reflex hyperventilation is attended by respiratory alkalosis.

In characteristic cases, hyperventilation is manifested by a sensation of numbness and prickling in the lips and skin on the face

and limbs, cold limbs, vertigo, tinnitus and tetany. A stuporous state gradually develops. Consciousness remains clear while the patient is in bed, but a typical vasodepressor syncope occurs as soon as he gets up.

Hyperventilation may lead to severe arrhythmias. The change of the pacemaker to the atrioventricular node or even to the ventricle with the development of atrioventricular, nodular or idioventricular rhythm is most commonly encountered. With cessation of hyperventilation the disorders of rhythm rapidly disappear. In cardiosclerosis these disorders of rhythm may prove stable and become an independent cause of loss of consciousness.

Hypoglycaemia of any origin produces symptoms similar to those consequent upon anoxia. Metabolic disorders develop in the brain in both cases, but they are caused by oxygen deficiency in one case and by a deficiency of the principal energy source in the other. Oxygen consumption by the brain diminishes sharply when the blood glucose falls below 30 mg/100 ml; diffuse slow waves are recorded on the EEG in such cases and the patient loses consciousness.

Disorders of cerebral cortical functions prevail in the clinical picture of hypoglycaemia in some cases, and affection mainly of the subcortical structures in others. Metabolic disorders in the brain are manifested as disorientation, amnesia and excitation which may terminate in delirium or unconsciousness. Affection of the vegetative nervous system causes weakness, perspiration, skin pallor and trembling.

Heart functions and regulation of the cardiovascular system suffer much less frequently. Cerebral anoxia may lead to arrhythmia and hypersensitivity of the heart to the vagus effect. Insulin noticeably intensifies the activity of the reflexes from the carotid sinus receptors. In our experience, loss of consciousness occurred in patients with the above noted signs of hypoglycaemia which pointed to affection of the central and vegetative nervous system. Other authors, however, emphasize that loss of consciousness may occur suddenly. It may be presumed that sudden loss of consciousness in such cases results from activation of the mechanisms of arrhythmic or sinocarotid syncope.

Hypoglycaemia with loss of consciousness is mostly encountered in patients with diabetes mellitus, congenital fructose intolerance, and in those with malignant and benign tumours. In some cases it is caused by insulin overdosage, in others by shifts in insulin consumption by tissues in different stages of the disease; the origin of these shifts is not known.

Sudden weakness is the earliest symptom of hypoglycaemia. All its other manifestations occur with no previously determined sequence. Moreover, the attacks of hypoglycaemia in the same patient

often differ sharply in the clinical picture. A picture of hemiparesis develops in one case, a convulsive seizure followed by a comatose state in another and diplopia with loss of memory and orientation in a third.

The multiform and inconstant clinical manifestations of hypoglycaemia make timely diagnosis of transient loss of consciousness caused by it very difficult. The clinical picture of this syndrome lacks even a single constant sign. Hypoglycaemia should therefore be considered in each case of unconsciousness of unknown aetiology and all clinicians recommend testing the blood serum for the content of glucose in every such instance.

A low blood glucose content is the cause of the hypoglycaemia syndrome and its only constant laboratory sign. The results of trial glucose therapy are of decisive diagnostic significance. All the clinical manifestations vanish immediately after intravenous glucose infusion only in cases which had developed due to hypoglycaemia.

Loss of consciousness sometimes occurs in drug addicts in the period of abstinence. A characteristic clinical picture of the syndrome develops in several hours or days after the narcotic had been discontinued. Unconsciousness usually occurs at the peak of the syndrome, i.e. approximately three days after alcohol or natural opium alkaloids are discontinued, by the end of 24 hours after barbiturates are discontinued and 8 to 12 hours after synthetic morphine preparations are discontinued.

Loss of consciousness in such cases is a consequence of impaired reflex regulation of peripheral circulation or is induced by deep metabolic disorders in the brain. The clinical picture of the episodes resembles that of vasodepressor syncope in some cases or is indistinguishable from an epileptic seizure in others.

The association of unconsciousness with deprivation of the habitual drug becomes obvious in most cases. This makes the diagnosis and the application of therapeutic measures much easier. After barbiturates are discontinued, some patients lose consciousness only when they change from a recumbent to an upright position. The patient does not lose consciousness when he is in bed. The association of unconsciousness with changes in the body position in space evidently indicates that arterial pressure regulation is impaired in the period of barbiturate abstinence. Inadequacy of arterial pressure regulation is possibly one of the consequences of metabolic disorders in the central nervous system.

Short-term loss of consciousness is among the clinical entities and arises due to the effect of many factors and have various mechanisms of development. The internist usually has to deal in his practice with patients who lose consciousness due to diffuse ischaemia of the brain consequent upon imperfect reflex regulation of

circulation, heart diseases or organic lesions of the arteries carrying blood to the brain.

Some of the syndromes arising in such cases have been studied quite well and have long been known under specific names such as simple syncope, the Adams-Stokes-Morgagni syndrome, orthostatic hypotension with spells of syncope. Other cases of characteristic loss of consciousness have been studied in less detail and possess no special clinical designation. It might possibly be expedient to apply the term 'syncope' to all cases of reversible transient loss of consciousness induced by factors producing an unfavourable effect on the central nervous system not directly, but via disorders of the function of the cardiovascular system.

The term 'attack' is now mainly used to designate loss of consciousness resulting from a primary disease of the brain, e.g. epilepsy; short-term loss of consciousness in some other cerebral diseases is often called 'syncope'. The manifestation of one and the same disease, e.g. hysteria, is sometimes called 'an attack' and at other times 'syncope'.

The main difficulty evidently consists not in the application of this or that term but in identifying the cause of the temporary loss of consciousness. This task is both responsible and difficult. A state of unconsciousness is almost always of a short duration. In most cases it begins and ends unwitnessed. Even when the state of unconsciousness occurs in the presence of other people one should not place great hopes on the testimony of eye witnesses. Being under the impression of the dramatic circumstances of the attack, they are usually incapable of accurately describing the manifestations of the disease.

A patient who had suffered from a transient spell of unconsciousness is usually examined in the period free of spells. The volume and diagnostic value of the information thus obtained depends to a very considerable degree on the skill showed in questioning the patient. Particular care should be taken to divulge information pertaining to the following points.

Had there ever been loss of consciousness in the past resembling the attack in question? A positive reply to this question indicates that the patient has one of many chronic diseases (epilepsy, narcolepsy, tetralogy of Fallot, the Wolff-Parkinson-White syndrome, etc.) in which attacks of transient loss of consciousness are a regular occurrence.

It is most vital to clarify the character of the patient's sensations immediately before and after the attack. Various types of aura and an initiating cry are very characteristic of epilepsy but are not encountered before syncope of cardiac origin. The latter often begin with palpitation which usually persists after consciousness is regained. Loss of consciousness in the aortic arch syndrome is usually

preceded by dizziness, pain in the back of the head, and visual disorders.

Simple syncope occurs suddenly and there is a sensation of warmth in the entire body and a peculiar euphoria after it ends. Disorientation, headache, amnesia and anomalous behaviour are often noted after grand mal epilepsy and after severe hypoglycaemia.

Arrhythmic syncope may occur both when the patient is asleep and when he is wide awake. Simple syncope does not occur during sleep. The association of short-term loss of consciousness with insulin injections, meals and sleep is characteristic of hypoglycaemia. These patients often develop signs of a syncope reaction and even lose consciousness in the morning after a long night's sleep or after any prolonged fasting. The disappearance of all the signs of the malady after a meal is characteristic of these patients.

Syncope caused by hyperventilation is always preceded by numbness of the lips and limbs which become cold with the sensation of being pricked with needles.

The cause of the loss of consciousness can sometimes be revealed by questioning the patient about the circumstances and the situation of its occurrence. In making the diagnosis of postural syncope, it is far from indifferent for the physician to know whether the patient had been lying or sitting up in bed before the syncope had occurred, whether he had been seated in the toilet or whether he had lost consciousness immediately on getting up from bed.

It is also necessary to ask whether syncope had taken place after a protracted stay in a stuffy room, after physical exercises, during emotional excitation or after a long fit of coughing. The association of hysteric syncope with emotional conflict and frequent loss of consciousness during physical exertion in aortic stenosis are generally known.

It is important to know of the patient's past and present diseases, the drugs he is taking and their dosage. It is also advisable to get a clear picture of the patient's appearance during the attack (the colour of the skin, whether urine had been passed or convulsions had occurred) by thoroughly questioning witnesses.

During physical examination of the patients it is essential to pay close attention to the subcutaneous veins, tendon reflexes, height of arterial pressure, the rate and rhythm of the heart beat and disorders of perspiration. Extreme trembling of the limbs is usually encountered in the abstinence syndrome and in patients who are under the effect of sympathomimetic agents.

Reflex reactions occurring in stimulation of the vagus nerves should be tested especially meticulously. Reactions to carotid sinus stimulation must be studied in every patient who had suffered an episode of loss of consciousness. The test may be carried out only if the pulse in both carotid arteries is good. The test is first carried

out with the patient in a recumbent position and only after that when he is in an upright position.

If stimulation of the carotid sinus induces syncope, the test with intravenous infusion of 2 mg of atropine must be carried out. The cardioinhibiting type of the carotid sinus syndrome is completely ruled out after the administration of this dose of atropine. Atropine does not prevent loss of consciousness in deficient blood supply to the brain in stenosis or occlusion of the carotid, vertebral or basilary arteries. During the atropine test it is necessary to measure the arterial pressure and record the ECG and EEG.

Syncope of the cardioinhibiting or vasodepressor type occurs in stimulation not only of the carotid sinus mechanoreceptors but also of the mechanoreceptors of many regions of the respiratory and digestive systems. We often encountered such syncope during bronchoscopy and gastroscopy. It is not spontaneous, but occurs only after stimulation of the afferent pathways contained in the vagus nerve. The prescription of atropine also prevents such syncope.

It is also recommended to test arterial pressure regulation in each case of syncope. The simplest method is Shelong's orthostatic test. The patient lies quietly in bed for 15 to 20 minutes with the cuff of a sphygmomanometer applied to the arm. In the last 10 minutes of this period his arterial pressure is measured by Korotkov's method and the pulse counted five or six times. The patient gets up quietly and stands without moving by the bed for 10 to 15 minutes during which his arterial pressure is measured and the pulse count taken six to eight times. The patient again lies down and arterial pressure is again measured and the pulse counted three or four times.

After a healthy person gets up his systolic arterial pressure decreases slightly (to 15 mm Hg) and for a short time. The heart beat increases by 20, rarely by 30 beats per minute. In patients with orthostatic hypotension the systolic and diastolic pressure drops markedly and the pulse pressure reduces. The rate of heart contractions increases much more than in a healthy person.

Disorders of postural arterial pressure regulation are detected particularly distinctly by the physical effort test. This test may be carried out on a bicycle ergometer, treadmill or by asking the patient to perform the act of squatting fully 20 times in 30 seconds. During these tests it is advisable to record the ECG continuously, for example, by means of a monitor. Serious disorders of the cardiac rhythm and marked hypotension may develop during and sometimes after these tests. The effort tests must be conducted with particular care in elderly patients and in patients with grave diseases of the cardiovascular system.

Many authors recommend the hyperventilation test. Our experience does not confirm its diagnostic value, however. This does

not apply to the hyperventilation test used sometimes in electroencephalography. The results of this functional examination are always jointly appraised with a neurologist.

Considerable diagnostic value should also be attached to the time it takes for syncope to develop. In metabolic disorders unconsciousness is usually not instantaneous; it seems to build up gradually and consciousness returns just as slowly. In narcolepsy and atrioventricular heart block unconsciousness occurs all of a sudden, its approach is not suspected not only by the people around the patient but by the patient himself. The habit and experience in interpreting the resultant data allows the cause of the transient loss of consciousness to be identified within a relatively short period of time in most cases and adequate therapy to be prescribed.

Supplement XXVI-1

Causes of Transient Loss of Consciousness

1. Vasodepression syncope.
2. Postural hypotension.
   - Orthostatic hypotension.
   - Idiopathic hypotension.
   - Shy-Drager's syndrome and other diseases of the peripheral and central nervous system.
   - Surgical sympathectomy.
   - Pharmacological desympathization.
3. Sharp reduction in circulating volume.
   - Varicose veins.
   - Compression of large veins by mobile tumours and enlarged uterus.
   - Diuretic therapy.
   - Removal of ascitic fluid.
   - Evacuation of the urinary bladder.
   - Pleural shock.
4. Mechanical obstacles to the flow of blood.
   - Heart myxoma.
   - Spherical thrombus of the heart.
5. Primary diseases of the nervous system.
   - Epilepsy.
     - Grand mal epilepsy.
     - Petit mal epilepsy.
     - Simple minor seizure.
     - Akinetic minor seizure.
     - Focal seizures (temporal epilepsy).
   - Concussion and contusion of the brain.
   - Tumour of the brain.
   - Narcolepsy.
   - Hysteria.
6. Increased carotid sinus activity.
   - Cardioinhibiting type.
   - Vasodepressor type.
7. Aortic arch syndrome.
   - Arteritis of the aorta and its branches.
   - Atherosclerosis of arteries arising from the aortic arch.
   - Dissecting aneurysm of the aorta.
8. Heart arrest and arrhythmias.
   - Disorders of cardiac conduction.
   - Disorder of sinoatrial conduction.
   - Disorder of atrioventricular conduction.
   - Complete heart block.
   - Incomplete heart block.
   - Supraventricular paroxysmal tachycardia.
   - Ventricular tachycardia.
   - Atrial fibrillation and flutter.
   - Wolff-Parkinson-White syndrome.
9. Pulmonary hypertension.
   - Embolism of the small branches of the pulmonary artery.
   - Primary pulmonary hypertension.
   - Secondary pulmonary hypertension.
   - Increased intrathoracic pressure.
10. Disorders of metabolism.
    - Hypoxaemia.
    - Hyperventilation.
    - Hypoglycaemia.
    - Abstinence syndrome.

Bibliography

Abbasi, A. S., MacAlpin, R. N., Eber, L. M., Pearce, M. L. *New Engl. J. Med.*, 1973, 289, 118-121

Akhrem-Akhremovich, R. M. Human Helminthoses. In *Manual of Internal Diseases.* Moscow, 1965, v. 5, p. 624-654 (in Russian)

Amoury, R. A. *Am. J. Surg.*, 1970, 119, 585-597

Aronov, D. M. *Coronary Insufficiency in the Young.* Moscow, 1974 (in Russian)

Atabek, A. A. Diabetes Insipidus. Moscow, 1951 (in Russian)

Balcon, R. Pacing. In *Recent Advances in Cardiology.* London, 1973, p. 363-372

Baldry, P. E. *The Battle against Heart Disease.* Cambridge, 1971

Bauer, J. *Differential Diagnosis of Internal Diseases.* London, 1967

Baum, G. L. *Textbook of Pulmonary Disease.* Boston, 1974, p. 201-218

Beevers, D. G., Brown, J. J., Ferris, J. B., et al. *Am. Heart J.*, 1973, 86, 404-415

Blaisdell, F. W., Lewis, F. B. Respiratory Distress Syndrome of Shock and Trauma. Philadelphia, 1977

Bloomenthal, E. D., Spellberg, M. A. *Am. J. Gastroenterol.*, 1971, 56, 334-341

Bluzhas, I. N., Babareskene, R. A. Lactate Dehydrogenase in the Diagnosis of Myocardial Infarction. In *Problems of Ischaemic Heart Disease.* Vilnius, 1976, p. 147-156 (in Russian)

Bockus, H. *Gastroenterology.* V. I-IV. Philadelphia, 1976

Böhme, H. *Der Herz und Geffässchall in Bild und Fon.* Leipzig, 1972, B. 192, S. 315-319

Bottinger, L. E., Westerhelm, B. *Acta. med. Scand.*, 1972, 192, 315-319

Bova, S. M. *Profuse Ulcer Haemorrhages.* Moscow, 1967 (in Russian)

Brown, J. J., Davis, D. L., Ferris, J. B. et al. *Brit. Med. J.*, 1972, 2, 729-734

Brown, J. J., Ferris, J. B., Fraser, R. et al. *Lancet*, 1972, 2, 243-247

Bruce, R. A., Hosmer, D. *Amer. Heart J.*, 1973, 85, 546-551

Burry, M. *Gut*, 1974, 15, 324-327

Capron, A., Yarzabel, L., Vernes, A. et al. *Path. Biol.*, 1970, 18, 357-365

Caracta, A. R., Damato, A. N., Gallagher, J. J. et al. *Am. J. Cardiol.*, 1973, 31, 245-253

Chaplin, H. Jr. *Progr. Hematol.*, 1973, 8, 25-49

Chatterjee, K., Heather, J. C. *Am. J. Med.*, 1968, 45, 643-648

Chazov, E. I., Kramer, A. A., Eventov, A. Z. et al. *Ter. arkh.*, 1977, 6, 12-25

Chernogorov, I. A. *Angina Pectoris.* Moscow, 1954 (in Russian)

Choinacki, B. *J. A. M. A.*, 1963, 186, 1176-1179

Claudio, M. P., Barrocas, M., Pifarre, R., et al. *Am. J. Cardiol.*, 1970, 25, 495-510

Coffman, J. D. *J. Lab. Clin. Med.* 1970, 76, 480-489

Coleman, R. E., Klein, M. S., Roberts, R., Sobel, B. E. *Am J. Cardiol.*, 1976, 37, 732-735

Cones, R. J. *Cardiogenic Shock.* New York, 1974

Coodley, E. Enzymes and Isoenzymes in Myocardial Infarction. In *Coronary Heart Disease.* Philadelphia, 1969, p. 123-131

Cooksley, W. G., Powell, L. W., Kerr, J. F. et al. *Am. J. Dig. Dis.*, 1972 17, 495-503

Cordes, L. G., Fraser, D. W. *Med. Clin. North America*, 1980, **64**, 3, 395-41
Crofton, J., Douglas, A. *Respiratory Diseases*. London, 1971
Damato, A. N., Lau, S. H. *Progr. Cardiovasc. Dis.*, 1970, **13**, 119-126
Denes, P., Rosen, K. *Circulation*, 1974, **50**, 861
Deterling, R. A., Clagett, O. T. *Circulation*, 1960, **21**, 710-721
Diamond, M. A., Murray, R. H., Schmid, P. G. *J. Clin. Invest.*, 1970, **4**
1341-1348
Engel, G. L. *Fainting*. Springfield, 1962
Erina, E. V. *Treatment of Hypertensive Disease*. Moscow, 1973 (in Russia
Fainshtein, F. E. *Aplastic and Hypoplastic Anaemias*. Moscow, 1965 (in Ru
sian)
Fanconi, G. *Semin. Hematol.*, 1964, **4**, 233-241
Feigenbaum, H. *Echocardiography*. Philadelphia, 1973
Feigenbaum, H., Corya, B., Dillon, J. C. et al. *Am. J. Cardiol.*, 1976, **3**
775-789
Feil, H., Siegel, M. L. *Am. J. Med. Sci.*, 1928, **175**, 255-261
Feruglio, G. A., Screenivasan, A. *Circulation*, 1959, **201**, 1087-1099
Finegold, S. M. *Anaerobic Bacteria in Human Disease*. New York, 1977
Finland, M. *Mod. Conc. Cardiovasc. Dis.*, 1972, **41**, 53-58
Fogelson, L. I. *Pains in the Region of the Heart and Behind the Sternum an
Their Significance in Expert Assessment of Working Capacity*. Moscow, 19
(in Russian)
Forledge, S. M. *Semin. Hematol.*, 1973, **10**, 327-337
Fraser, R. G., Pare, J. A. *Diagnosis of Diseases of the Chest*. Philadelphi
1970
French, H. *An Index of Differential Diagnosis*. Bristol, 1973
Friedberg, C. K. *Diseases of the Heart*. Philadelphia, London, 1966
Gallavardin, L. *Prat. Med. Franc.*, 1932, **13**, 19-31
Garraty, G., Petz, L. D. *Am. J. Med.*, 1975, **58**, 398-407
Gell, P. G. H., Coombs, R. R. A., Lachman, P. J. *Clinical Aspects of Immu
nology*. Oxford, 1976
Genes, S. G. (Ed.). *Manual of Endocrinology*. Moscow, 1973 (in Russian)
Gibson, D. Echocardiography. In *Recent Advances in Cardiology*. London
1973, p. 266-278
Gimpert, E., Jakob, M., Hitzig, W. H. *Blood*, 1975, **45**, 71-82
Glaz, E., Vecsel, P. *Aldosterone*. Budapest, 1972
Goodman, L. S., Gilman, A. *The Pharmacological Basis of Therapeutics*. Ne
York, 1960
Goryanina, N. K., Shcherba, S. G. *Kardiol.*, 1964, **5**, 25-31
Gukasyan, A. G. *Constipation and Its Management*. Moscow, 1959, 158 (in Rus
sian)
Hambry, R. I., Gulotta, S. J. *Am. Heart J.*, 1967, **74**, 110-121
Hansing, C. E., Rowe, G. G. *Circulation*, 1972, **45**, 763-777
Harvey, A. M., Bordley, J. *Differential Diagnosis*. Philadelphia, 1970
Hegglin, R. *Differentialdiagnose inneier Krankheiten*. Stuttgart, 1961
Herschman, S. Z., Hammer, G. S. *Am. J. Cardiol.*, 1974, **34**, 224-231
Hoffman, B. F., Cranefield, P. F. *Amer. J. Med.*, 1964, **37**, 670-682
Hohl, R. D., Frame, B., Schaltz, I. J. *Am. J. Med.*, 1965, **39**, 134-141
Hurst, J. E. (Ed.). *The Heart*. New York, 1974
Huxley, E. J., Viroslav, J., Gray, W. R. et al. *Amer. J. Med.*, 1978, **64**, 564
568
Ilyinsky, Yu. A. *Ornithosis*. Moscow, 1974 (in Russian)
Istamanova, T. S. *Functional Disorders of Internal Organs in Neurasthenia*
Moscow, 1958 (in Russian)
Ivanitskaya, M. A. (Ed.). *Roentgenological Diagnosis of Cardiovascular Dis
eases*. Moscow, 1970 (in Russian)

Jio, M., Yamada, H., Kitani, K., Sasaki, Y. *Nuclear Hepatology*. Stuttgart, 1974
Johanson, W. G., Pierce, A. K., Sanford, J. P. et al. *Ann. Intern. Med.*, 1972, 77, 701-706
Jones, F. A., Godding, E. *Management of Constipation*. Oxford, 1972
Jones, P. F. *Emergency Abdominal Surgery in Infancy, Childhood and Adult Life*. Oxford, 1974
Kaplan, H. S. *Hodgkin's Disease*. Cambridge, 1972
Karavanov, A. G., Danilov, I. V. *Errors in Diagnosis and Treatment of Acute Abdominal Diseases and Injuries*. Kiev, 1975 (in Russian)
Kattus, A. *Am. J. Cardiol.*, 1974, 33, 721-729
Katz, M., Lee, S. K., Cooper, B. *New Engl. J. Med.*, 1972, 287, 425-432
Kawai, T. *Clinical Aspects of the Plasma Proteins*. Tokyo, 1973
Kazantsev, A. P. *Ter. arkh.*, 1981, 3, 16-22
Khanina, S. B., Shirinskaya, G. I. *Functional Cardiopathies*. Moscow, 1971 (in Russian)
Kirkendall, W. M., Overturf, M. *Mod. Conc. Cardiovasc. Dis.*, 1973, 17, 47-54
Knyazhetsky, S. M. *Manual of Tuberculosis of the Respiratory Organs*. Leningrad, 1972 (in Russian)
Korovin, A. M. *Paroxysmal Disorders of Consciousness*. Leningrad, 1973 (in Russian)
Krantz, S. B. *Brit. J. Haemat.*, 1973, 25, 1-15
Kshanovsky, S. A. *Differential Diagnosis of Pulmonary Tuberculosis in Children and Adolescents*. Kiev, 1974 (in Russian)
Kushner, J. P., Lee, G. R., Wintrobe, M. M., Cartwright, C. *Medicine*, 1971, 50, 139-151
Leatham, A. *Auscultation of the Heart and Phonocardiography*. London, 1975
Leavel, B. S., Thorup, O. *Fundamentals of Clinical Hematology*. Philadelphia, 1976
Lenegre, J. *Progr. Cardiovasc. Dis.*, 1974, 6, 317-329
Levitan, M. Kh., Abasov, I. T., Kapuller, L. L. *Crohn's Disease*. Baku, 1974 (in Russian)
Loris, I. F. *Diseases of the Intestine*. Moscow, 1957 (in Russian)
Lukyanchenko, B. Ya. *Diagnosis of Tumours and Cysts of the Mediastinum*. Moscow, 1958 (in Russian)
Luzzatto, L. *Clin. Haematol.*, 1975, 4, 83-86
MacBryde, C. M., Blacklow, R. S. *Signs and Symptoms*. Philadelphia, 1970
McCoombs, R. P. *Fundamentals of Internal Medicine*. Chicago, 1971
MacKenzie, I. L., Donaldson, R. M., Trier, J. S. et al. *New Engl. J. Med.*, 1972, 286, 1021-1024
McLaughlin, P., Coats, G., Wood, D. et al. *Am. J. Cardiol.*, 1975, 35, 390-405
McLouglin, M., Colapinto, R., Hobbs, B. *J. A. M. A.*, 1975, 232, 1238-1246
Maldonado, J. E., Taswell, H. F. *Blood*, 1974, 44, 495-501
Mann, R. B., Jaffe, E. S., Braylan, R. C. et al. *New Engl. J. Med.*, 1976. 295, 685-697
Mansurov, Kh. Kh. Diseases of the Hepatic Vessels. In *Manual of Internal Diseases*. Moscow, 1965, v. 5, p. 478-489 (in Russian)
Marmont, A., Peschle, C., Sanguineti, H. et al. *Blood*, 1975, 45, 247-252
Marriot, H. *Geriatrics*, 1970, 25, 91-102
Mazaev, P. N., Kostyuchenok, B. M., Grishkevich, A. M. *X-ray Diagnosis of Tricuspid Valvular Disease*. Moscow, 1971 (in Russian)
Mazhdrakov, G., Popov, N. (Eds.). *Diseases of the Kidneys*. Sofia, 1976
Menshikov, V. V., Kalinina, A. I., Zhdanova, S. M. et al. *Pheochromocytoma*. Moscow, 1965 (in Russian)
Mikhailov, A. A. Clinical and Haemodynamic Characteristics of Different Forms of Hypertensive Disease and the Renal Hypertension Syndrome. Diss. Moscow, 1973 (in Russian)

Moiseev, S. G. *Acute Internal Diseases.* Moscow, 1971 (in Russian)
Molchanov, N. S. *Acute Pneumonias.* Leningrad, 1965 (in Russian)
Narula, O. S. *Circulation*, 1974, 50, 1129-1137
Nasonova, V. A. *Systemic Lupus Erythematosus.* Moscow, 1972 (in Russian)
Nasser, W. K., Davis, R. H., Dillon, J. C. et al. *Am. Heart J.*, 1972, 33, 694-699
Nechaev, D. D., Zhorova, I. I., Levina, G. A., Tarichko, Yu. V. *Kardiologiya*, 1977, 3, 83-89
Neill, C., Mounsey, P. *Brit. Heart J.*, 1958, 20, 61-74
Olesen, K. H., Warburg, E. *Acta med. Spand.*, 1958, 160, 437-441
Orlova, P. N., Shkhvatsabaya, L. V. *Klin. med.*, 1977, 8, 45-52
O'Sullivan, J. P., Wilding, R. P. *Brit. Med. J.*, 1974, 3, 7-13
Patsiora, M. D. *Surgery of Portal Hypertension.* Moscow, 1974 (in Russian)
Patterson, R. (Ed.). *Allergic Diseases.* Philadelphia, 1972
Perloff, J. K. *The Clinical Recognition of Congenital Heart Disease.* Philadelphia, 1970
Petrosyan, Yu. S., Zingerman, L. S. *Ter. arkh.*, 1977, 6, 16-21
Petrov, I. I. Clinical and Immunological Characteristics of the Hypertensive Form of Chronic Glomerulonephritis. Diss. Moscow, 1974 (in Russian)
Petrovsky, B. V., Belichenko, I. A., Krylov, V. S. *Surgery of the Aortic Arch Branches.* Moscow, 1970 (in Russian)
Pevzner, M. I. *Chronic Diseases of the Stomach and Intestine.* Moscow, 1940 (in Russian)
Pitt, B., Strauss, H. W. *Am. J. Cardiol.*, 1976, 37, 797-803
Pocock, W. A., Barlow, J. B. *Am. J. Cardiol.*, 1971, 51, 731-742
Podonenko-Bogdanova, A. P. *Diseases Simulating Acute Abdomen.* Kiev, 1968 (in Russian)
Popov, V. G., Topolyansky, V. D. *Pulmonary Oedema.* Moscow, 1975 (in Russian)
Rabkin, I. Kh. *Roentgenosemiotics of Pulmonary Hypertension.* Moscow, 1967 (in Russian)
Rabukhin, A. E., Dobrokhotova, M. N., Tanitrova, N. S. *Sarcoidosis.* Moscow, 1975 (in Russian)
Ratner, N. A. Involvement of the Kidneys in Endocrine and Obstetric Pathology. In *Fundamentals of Nephrology.* Moscow, 1972, v. 2, p. 712-721 (in Russian)
Ratner, N. A., Gerasimova, E. N., Gerasimenko, P. P. *Hyperaldosteronism.* Moscow, 1968 (in Russian)
Realini, S., Hoffstetter, J. R. *Schweiz. med. Wschr.*, 1972, 102, 565-571
Redwood, D. R., Scherer, J. L., Epstein, S. *Circulation*, 1974, 49, 116-1122
Romsey, H. W., Elliott, L. P., Bartley, T. D. et al. *Arch. Int. Med.*, 1969, 124, 206-218
Rubinshtein, G. R. *Differential Diagnosis of Pulmonary Diseases.* V. 1-2. Moscow, 1949-1950 (in Russian)
Ruda, M. Ya., Pichugin, V. N., Staroverov, I. I. *Ter. arkh.*, 1977, 6, 21-32
Rusanov, M. N. *Klin. med.*, 1975, 1, 122-141
Schiff, L. *Diseases of the Liver.* Philadelphia, 1969
Schiff, L. Jaundice. In *Signs and Symptoms.* Philadelphia, 1970, p. 399-427
Sealey, J. E., Buhler, F. R., Laragh, J., Vaughan, E. *Am. J. Med.*, 1973, 55, 391-405
Seneca, H., Grant, J. Chemotherapy. In *Antibiotics and Chemotherapy.* Basel 1976, v. 21, p. 77-86
Shelagurov, A. A. *Diseases of the Pancreas.* Moscow, 1970 (in Russian)
Shishkin, S. S. *Repeated Myocardial Infarctions.* Moscow, 1963 (in Russian)
Shteingardt, Y. N., Ageeva, T. S. *Ter. arkh.*, 1981, 5, 110-112
Silvestrov, V. P. *Non-resolving Pneumonias and Their Treatment.* Leningrad 1968 (in Russian)

Sirchia, G., Lewis, S. M. *Clin. Haemat.*, 1975, 4, 199-208
Sjostrom, R. Acute Terminal Ileitis and Its Relation to Crohn Disease. In *Regional Enteritis.* Stockholm, 1971, p. 73-78
Smolyannikov, A. V., Naddachina, T. A. *Problems of Pathological Anatomy and Pathogenesis of Coronary Insufficiency.* Moscow, 1968 (in Russian)
Smotrov, V. N. *Chronic Colitis.* Moscow, 1934 (in Russian)
Sokolov, L. K. *Atlas of Stomach and Duodenal Endoscopy.* Moscow, 1975 (in Russian)
Strickland, B. *Brit. J. Radiol.*, 1967, 40, 930-939
Sumarkov, A. V., Mikhailov, A. A. *Cardiac Arrhythmias.* Moscow, 1976 (in Russian)
Sumarkov, A. V., Moiseev, V. S., Mikhailov, A. A. et al. *The Recognition of Heart Diseases.* Tashkent, 1976 (in Russian)
Tareev, E. M. *Collagenoses.* Moscow, 1965 (in Russian)
Tareev, E. M. Ed. *Fundamentals of Nephrology.* V. 1-2. Moscow, 1972 (in Russian)
Tareev, E. M., Afanasyeva, K. A. Malignant Tumours of the Liver. In *Manual of Internal Diseases.* Moscow, 1965, v. 5, p. 494-505 (in Russian)
Teore, D. *Brit. Heart J.*, 1958, 20, 1-9
Tetelbaum, A. G. *Clinical Types and Forms of Angina Pectoris and the Onset of Myocardial Infarction.* Moscow, 1960 (in Russian)
Uglov, F. G. *Pulmonary Carcinoma.* Leningrad, 1962 (in Russian)
Vasilenko, V. Kh. *Acquired Heart Diseases.* Kiev, 1972, p. 304 (in Russian)
Vinner, M. G., Shulutko, M. L. *Spherical Growths in the Lungs.* Sverdlovsk, 1971, p. 307 (in Russian)
Vinogradov, A. V. *Ter. arkh.*, 1951, 2, 48-53
Vinogradov, A. V. *Ter. arkh.*, 1952, 1, 76-81
Vinogradov, A. V. *Sov. med.*, 1954, 1, 17-23
Vinogradov, A. V. *Kazansk. med. zh.*, 1959, 9, 6-12
Vinogradov, A. V., Glezer, G. A., Zhdanov, V. S. *Errors in the Diagnosis of Heart Diseases.* Moscow, 1973, p. 192 (in Russian)
Vinogradov, A. V., Vikhert, A. M., Dorofeeva, Z. Z., Chazov, E. I. *Myocardial Infarction.* Moscow, 1971, p. 311 (in Russian)
Volynski, Yu. D. *Changes in Intracardiac Haemodynamics in Heart Diseases.* Moscow, 1969, p. 261 (in Russian)
Vorobyev, A. I., Shishkova, T. V. *Cardialgia.* Moscow, 1973, p. 136 (in Russian)
Waldenström, J. *Diagnosis and Treatment of Multiple Myeloma.* New York, 1970
Wallace, R., Musher, D., Martin, R. *Amer. J. Med.*, 1978, 64, 87-93
Watts, H. D., Admirand, W. H. *J. A. M. A.*, 1974, 230, 1974-1986
Webb, S. F., Vall-Spinosa, A. *Chest*, 1975, 68, 703-708
Wolstenholme, G. E. W., O'Connor, M. (Eds.). *Hypertrophic Obstructive Cardiomyopathy.* London, 1971
Yablokov, D. D. *Pulmonary Haemorrhages.* Novosibirsk, 1944 (in Russian)
Yoshida, A. *Science*, 1973, 179, 532-541
Yudin, I. Yu. *Non-specific Ulcerative Colitis.* Moscow, 1968 (in Russian)
Yurenev, P. N., Semenovich, I. I. *Clinical Picture and Treatment of Allergic Affections of the Heart and Vessels.* Moscow, 1972 (in Russian)
Zarnoza, J., Goldman, A. M. Wallace, S. et al. *Amer. J. Roentgen*, 1976, 127, 989-996
Zemlyanoi, A. G. *Diverticula of the Gastro-intestinal Tract.* Leningrad, 1970, p. 238 (in Russian)
Zubarev, R. P. *Ebstein's Anomaly.* Moscow, 1975 (in Russian)

Subject Index

abdomen, acute diabetic, 37
  distension, 126
  enlargement, causes, 141
  flatulence, 127
  muscles, rigidity, 18f, 22
  pain, *see* abdominal pain
abdominal angina, 30
abdominal pain, 16ff
  in acute gastritis and enteritis, 27
  in amoebiasis, 269
  in appendicitis, 27ff
  causes, 41
  in cholelithiasis, 21
  in Crohn's disease, 32, 268
  in diabetes mellitus, 37
  diffuse, 17
  in gynaecological diseases, 29f
  in haemorrhagic vasculitis, 36
  in heart diseases, 20
  intensity, 16
  in liver necrosis, 26
  localized, 17
  in lung and pleural diseases, 18
  in mesadenitis, 31
  in myocardial infarction, 20
  in pancreatitis, 23, 34f
  in perforation of hollow organs, 22
  in periodical disease, 35
  in pneumonia, 18ff
  in porphyria, 31
  referred, 16
  somatic, 16
  in tabes dorsalis, 40
  in tuberculous ileotyphlitis, 276
  in ulcerative colitis, 265
  visceral, 16
acidosis tubular, 724
acrocyanosis, 626
acromegaly, 719
adiposity, 398
adrenal, adenocarcinoma, 116
  cortex tumour and hypertension, 93
alpha-1-antitrypsin deficiency, 509
alpha-fetoprotein, 516, 518
alveolitis, diffuse fibroplastic, 702
amoebiasis, 268f, 360
  differential diagnosis, 269, 277
amyloidosis, 580, 745
  familial, 583
  secondary, 580ff
anaemia(s), 42ff
  aplastic, 55, 57, 529
  in carcinoma metastasis to bone marrow, 58f
  causes, 68
  Cooley's, 539
  in folic acid deficiency, 50, 57
  after gastrectomy, 48, 58
haemolytic, 59ff, 745
  acquired, 64, 539
  angiopathic, 67
  autoimmune, 64, 740
  with cold antibodies, 65
  congenital, 59
  drug, 68
  microangiopathic, 67
  with warm antibodies, 65
  hypochromic microcytic, 53
  hypoplastic, 55f
  in intracellular enzyme deficiency, 60f
  iron-deficiency, 52, 54, 596
  non-spherocytic, 61, 537
  pernicious, 46, 59
  in protein deficiency, 45ff, 50, 57
  pseudoplastic, 55f
  in red cell destruction, 67
  sickle-cell, 61f, 538
  sideroblastic, 54, 57, 506, 522, 525
  in thalassaemia, 63
  in vitamin B_{12} deficiency, 45ff, 50, 57
anal fissures, 246
angina pectoris, 144ff, 187
  causes, 144
  classical form, 144f
  clinical picture, 146
  creatine phosphokinase activity, 156
  dysadaptational, 148
  of effort, 145ff
  exercise test(s), 151
  fresh, 146
  pain in, 145
  peripheral, 146, 186
  scintigraphy in, 155

angina pectoris
specific form, 144, 149
stable, 147
unstable, 148
aorta, arch, aneurysm, 179
ascending, dissecting aneurysm, 219, 221ff, 226, 229, 306
atherosclerosis, 444
descending, dissecting aneurysm, 223ff, 226f, 229, 306, 633
thoracic, aneurysm, 179, 189, 228ff, 306, 455, 633
differential diagnosis, 221, 226, 229
ECG, 223
echocardiogram, 222
haemoptysis, 307
heart sounds, 230
murmurs, 222, 230, 468
pain, 221, 223f, 229
rupture, 227f, 383
aortalgia, 178
aortic insufficiency, 422, 443, 448ff, 454f, 458, 612
acute, 454
and aortic stenosis, 454
after aortic valve prosthetics, 453
chronic, 448
congenital, 448, 453,
in endocarditis, 452, 454
iatrogenic, 453
and mitral stenosis, 451
murmur, 449, 451ff, 469, 488
rheumatic, 448f
syphilitic, 449f, 452
aortic stenosis, 410, 412, 439ff, 448, 467, 477, 611
congenital, 474ff
differential diagnosis, aortic insufficiency, 443
aortic coarctation, 445
mitral insufficiency, 488
mitral stenosis, 442f
myocardial infarction, 445
pulmonary artery stenosis, 444
subaortic stenosis, 446
ventricular septal defect, 444
ECG, 445
heart failure in, 439
heart sounds, 476f
murmur(s), 437, 441f, 444, 474
signs, 440f
subvalvular, 476
supravalvular, 476
valvular, 474
aortitis, 178, 306
syphilitic, 178, 444
aplastic crises, 60
appendicitis acute, 17f, 27ff, 30
differential diagnosis, Crohn's disease, 33
mesadenitis acute, 34
renal colic, 38f
arrhythmias, 71ff
mechanisms of development, 72
sinus, 73
types, 87
arterial hypertension, 88ff, 95ff, 100ff
in adrenal adenocarcinoma, 116
in aortic arteritis and coarctation, 109f
auxiliary diagnostic methods, 94
benign, 88, 90, 94f
in catecholamine hypersecretion, 119
causes, 123
and Conn's syndrome, 114
in diabetic glomerulosclerosis, 101
diastolic, 88
differential diagnosis, clinical criteria, 92
drug, 122
endocrine, 114ff
essential, *see also* hypertensive disease, 88, 93
in haemangiopericytoma, 119
idiopathic, 88
in Itsenko-Cushing's syndrome, 117
malignant, 88, 94, 96
in mineralocorticoid hypersecretion, 117
oedema in, 93
paroxysmal, 93
in periarteritis nodosa, 113
in phaeochromocytoma, 120
in polycystic renal disease, 100
and pyelonephritis, 95
renal, 94ff
in renal artery diseases, 107, 109
renovascular, 105
symptomatic, 88, 90, 92ff, 106
systolic, 88
in urinary syndrome, 103
in Wilm's tumour, 119
arteriovenous aneurysms in systemic circulation, 467
ascites, 124ff, 507, 515, 520, 526f
abdominal percussion in, 124
causes, 128, 141
chyliform, 125, 139
in constrictive pericarditis, 137
differential diagnosis, 140
in gastro-intestinal diseases, 139
in heart failure, 137, 139
in heart and pericardium diseases, 138

ascites
identification, 126
in kidney diseases, 138
in liver diseases, 134
in mesothelioma, 129
in myxoedema, 140
in nephrotic syndrome, 138
in pancreatitis, 140
in peritoneal pseudomyxoma, 130
in portal hypertension, 131
in tuberculous peritonitis, 128
ascitic fluid, 125
asthma, bronchial, *see* bronchial asthma
cardiac, 609ff
atherosclerosis and hypertensive disease, 103
atrial, fibrillation, 79
flutter, 77, 79, 83
myxoma, 760
septal defect, 416, 425, 481, 776
ECG, 482
heart failure in, 425
heart sounds, 472
murmurs, 481, 489
X-ray, 482
atrioventricular, block, 86
conduction, delayed, 84

bacillary dysentery, 267, 361
differential diagnosis, functional diarrhoea, 291
ulcerative colitis, 268
bacteraemia, 314
balantidiasis, 270, 361
begascosis, 667
bile duct(s), obstruction, 555, 557f
tumours, 559
biliary cirrhosis, primary, 549, 553, 555
bilirubin, 536
conjugated, 542
unconjugated, 536, 540, 542
blood enzyme activity, 207
blood shunt, 464
bloody vomiting, 345, 347
differentiation from haemoptysis, 375
bradycardia, sinus, 73
bronchi, adenoma, 379, 686
carcinoma, 188, 299, 636, 684
obstruction, paroxysmal dyspnoea in, 607
tumours, 378, 704
bronchial asthma, 605ff, 610
atopic, 605
mixed, 605
bronchiectases, 327, 378
bronchitis, 377, 607
bronchoadenitis, 301
bronchopulmonary aspergillosis, 606
bronchospasm, drug-induced, 606
brucellosis, 322f
bundle branch block, 81, 205
Burkitt's lymphoma, 296
burn shock, 350
Burnet's test, 322

carbohydrate intolerance, 285
carcinoid tumour, 392ff
carcinosis, miliary, 699
cardiac fibrillation, 80ff, 413f
cardiac glycosides, 71, 77, 81, 85
cardialgia, 144, 186
non-coronarogenic, 157
cardiomyopathy, 400, 473, 476, 484, 611
congestive, 381, 399, 403, 410
differential diagnosis, 217, 404
ECG, 218, 401, 406
heart sounds, 404
murmurs, 404
restrictive, 399, 507
cardiopathy, climacteric, 162
ECG, 165
functional, 158
pain in, 163
cardiosclerosis, atherosclerotic, 407, 469
postinfarction, 610
cardiogenic shock, 350
carditis, rheumatic, 175
carotid sinus, 768
Castle's intrinsic factor, 45f, 48
catecholamine hypersecretion, 119
cat's purr, 490
cervical osteochondrosis, 187, 190
chest pain, 143ff, 188
in angina pectoris, 145
in cardiomyopathy, 217
causes, 233
in diseases of aorta, 219
in dry pleurisy, 232
in fibromyositis, 185
in herpes zoster, 184
intolerable, 193f, 200, 216f, 219, 230f
in mammary gland diseases, 192
in myocarditis, 216
in periodical disease, 232
in pleurodynia, 232
chill(s), 311, 337
recurrent, 312
cholangioma, 514f
cholangitis, 325, 560
purulent, 326
cholecystitis calculous, 60
cholelithiasis, 556f

cholestasis intrahepatic, 547
chordae tendinae, 430
  rupture, 435, 437f
chromophobic pituitary adenoma, 371
chylothorax, 633
Clauvert's cups, 126
coagulation, intravascular, 740
coagulopathy, utilization, 740
cobalamines, 46
coeliac disease, 49, 52, 139, 285, 594ff, 599, 602
  clinical signs, 595
  diarrhoea in, 255
  differential diagnosis, alimentary dystrophy, 597
    chronic enteritis, 281
    diffuse lymphosarcoma of small intestine, 599
    heart failure, 597
    intestinal lymphangiectasis, 597
    Whipple's disease, 602
  X-ray signs, 596
colic, hepatic, 21, 555f
  mucous, 291
  renal, 38f, 711
colitis, 277, 279
  granulomatous, *see* granulomatous colitis
  ulcerative, *see* ulcerative colitis
collagenosis, 328
colon, congenital aganglionosis, 238
  malignant tumours, 359
connective tissue, diffuse diseases, 623, 640
consciousness loss, transient, *see also* syncope, 749ff
  in acute circulatory insufficiency, 751
  in arrhythmias, 772, 780
  in blood flow obstruction, 759
  in brain contusion, concussion, tumours, 764
  in carotid sinus increased activity, 768, 781
  causes, 782
    identification, 779ff
  in circulation volume diminution, 757ff
  in congenital heart diseases, 776
  in drug abstinence, 778
  in epilepsy, 761
  in heart arrest, 472
  in hyperventilation, 776, 780
  in Meniére's syndrome, 765
  in metabolic disorders, 776
  in pleural shock, 759
  in pulmonary hypertension, 776
constipation, 235ff
  in adenocarcinoma of large intestine, 242
  causes, 236
  differential diagnosis, 241
  in diverticulosis of large intestine, 243
  drug, 248
  endocrinic, 248,
  in Hirschsprung's disease, 238
  mechanical, 241
  metabolic, 248
  muscular, 249
  in pregnancy, 248
  psychogenic, 246
  simple, 236
  in stricture of large intestine, 245
  toxic, 248
  types, 250
  in ulcerative colitis, 265
coproliths, 244
coprostasis, 244
coronary arteriovenous aneurysm, 467
cor pulmonale, 396ff, 610
  causes, 459
Courvoisier's law, 557
creatine phosphokinase, 207, 209
Crohn's disease, 32f, 139, 261, 276, 286, 330
  biopsy, 310
  diarrhoea in, 262, 283
  differential diagnosis, acute appendicitis, 33
    chronic enteritis, 283
  intestinal haemorrhage in, 360, 362
cryoglobulinaemia essential, 745
cryoglobulins, 625

de Mussef's sign, 487
diabetes, insipidus, 719
  mellitus, 507, 718
  nephrogenic, 721
  pituitary, 720
diaphragm, upward displacement, 631
diaphragmatic hernia, 183
diarrhoea, 252, 291
  in amoebiasis, 268
  in bacillary dysentery, 267
  in carcinoid tumour, 258
  causes, 292
  Cochin-China, 381
  in coeliac disease, 595
  in Crohn's disease, 261f, 283
  in enteritis, 278
  functional, 289
    differential diagnosis, 291
  in gastrinoma, 255
  in helminth infestations, 280

diarrhoea
in intestinal diseases, 252
in intestinal obstruction, 274
in pancreatic cholera, 256
differential diagnosis, method, 11ff
disaccharidase deficiency, 285f, 289, 291
tests for, 287f
disease(s), Addison's *see also* anaemia, pernicious, 85
aorto-mitral, 422, 441
Basedow's 368, 370
Bekker's 407
blood, 527ff
Brill-Symmer's 297
coeliac, *see* coeliac disease
Crohn's *see* Crohn's disease
Davis', 407
Ebstein's, 473
Filatov's, 545
Gaucher's, 510
Glanzmann's, 745
of haematopoietic organs, 527ff
Hashimoto's, 372
Hirschsprung's, 238
Itsenko-Cushing's, 719
Konovalov-Wilson's, 501, 508
legionnaires', 655
Marchiafa-Micheli, 539
Moschcowitz's 740, 742
periodical, *see* periodical disease,
Raynaud's 619
Rendu-Weber-Osler, 744
veno-occlusive, 527
Werlhof's *see also* purpura, thrombocytopenic, 133, 738
Whipple's, 139, 600
differential diagnosis, 602f
drug intolerance and fever, 335
duodenum, diverticulum, 351
dyserythropoiesis, congenital, 57
dyspnoea paroxysmal, 605ff
in bronchial obstruction, 607
in cardiovascular diseases, 608ff
causes, 618
in hypertensive disease, 610
in lung diseases, 605ff
in nephritis, 616
in obstructive pulmonary emphysema, 607
in periarteritis nodosa, 614
in spontaneous pneumothorax, 607
in tachycardia, 613
dystonia neurocirculatory, 158, 163, 175
pain in, 159
differentiation from angina pectoris, 160
dystrophy alimentary, 593
differentiation from coeliac disease, 597

Ebstein's anomaly, 388
ejection sound, 476
elliptocytosis congenital, 60
endocarditis, bacterial, 314ff, 319, 454, 579
fibroplastic parietal, 407
lenta, 316ff, 471
Libman-Sacks, 450
rheumatic, 175, 470
endometriosis, 242
enteritis, chronic, 277f, 283
diarrhoea in, 277
differential diagnosis, 281ff
regional, 261f
segmental, *see also* Crohn's disease, 261
enterocolitis, 278
differentiation from dysentery, 279
tuberculous, 361
enteropathy, gluten, *see* coeliac disease
with excessive protein loss, 43f, 603
epilepsy, 761f, 774, 779
ergot preparations, 625
erythropoiesis ineffective, 56f
excretion nephrosis, 584
exercise test, 151f
false positive result, 154
extrasystole(s), 74, 197
atrial, 74, 83
atrioventricular, 74f
ventricular, 75, 83
exudate, 125, 632
enzyme deficiency, intracellular, 60f

fever, 308, 523
artificial, 308f
in blood disease, 334
in bronchiectases, 327
in brucellosis, 322
causes, 336
in cholangitis, 325
in collagenoses, 328
in Crohn's disease, 330
drug, 328, 335
familial Mediterranean, *see* periodical disease
in focal infections, 324
in general infection, 313
in heart failure, 318
infectious, 311
long-term, 308, 310, 319
causes, 309

fever
in malaria, 312, 325
rheumatic, 414, 450, 641
in rheumatic heart disease, 317
in rheumatoid arthritis, 328
in systemic lupus erythematosus, 328
in tuberculosis, 319
in tumours, 330
of unknown origin, 308ff
examination of patients, 309
trial therapy, 310
fibroelastosis endocardial, 407ff, 413, 470, 473
fibromyositis, 185
fibrosis endocardial, 407
flushes in carcinoid syndrome, 258
folic acid, 49
deficiency, 45, 49f, 57
anaemia in, 50
causes, 70

gallop rhythm 82, 218, 476
gastrinoma, 252f
diagnostic tests, 253
differential diagnosis, carcinoid syndrome, 260
coeliac disease, 255
pancreatic cholera, 257
peptic ulcer, 254
gastritis, 349
gastroenteritis, 127
eosinophilic, 139
gastro-intestinal haemorrhage, 345ff, 524ff
aetiology, 347
causes, 347, 365
in congenital telangiectases, 352
in diaphragmatic hernia, 354
differential diagnosis, 362
in diverticulum of intestine, 351f
in duodenal diverticula, 351
endoscopy in, 349, 351
in gastritis, 349
massive, 345
in Meckel's diverticulum, 325
in peptic ulcer, 349
in pseudoxanthoma elasticum, 353
in varicose veins of oesophagus, 355
glomerulonephritis, 572f, 576
and arterial hypertension, 102f
in bacterial endocarditis, 579
chronic, 102
kidney biopsy in, 104
in rheumatoid disease, 576
urinary syndrome in, 104
glomerulosclerosis diabetic, 587
and arterial hypertension, 101
goitre, diffuse or nodular, 334, 367f
intrathoracic, 304f
mediastinal, 304
mixed, 367
toxic, 367
granulomatous colitis, *see also* Crohn's disease, 261f, 264, 270
differential diagnosis, carcinoma of large intestine, 274
ulcerative colitis, 272

haem, 51, 59
haemangiopericytoma, 119
haematosarcoma, 297, 299f, 305, 310, 332, 634, 639
haemochromatosis, 506ff, 510
haemoglobin, foetal, 539
S, 538
unstable, 64
haemoglobinopathies, 61
haemoglobinuria, march, 67
paroxysmal, cold, 66
nocturnal, *see also* syndrome, Marchiafava-Micheli, 66, 539
haemolytic jaundice, *see also* anaemia, haemolytic, 536f, 542
haemophilia, 353
haemoptysis, 375f, 413f, 697
in bronchiectasis, 378
in bronchitis, 377
causes, 383
differentiation from bloody vomiting, 375
false, 377
in pulmonary carcinoma, 378
in pulmonary tuberculosis, 379
haemorrhoids, 245, 358, 362
haemothorax, 633
heart amyloidosis, 411f
heart arrest and loss of consciousness, 772
heart failure, 131, 384, 391ff, 395, 399, 401, 403, 405, 410f, 456f, 576, 601, 714
biventricular, 399, 406, 412
causes, 458
left-ventricular, 402, 409, 411, 413, 439, 456f
right-ventricular, 25ff, 384, 386ff, 394, 398, 402, 406ff, 411, 414, 439, 451, 455, 504, 531, 610
heart murmur(s), 461ff
abdominal, 464
continuous, 461f, 466
causes, 494
diastolic, 461, 481, 484f, 488f, 491
early, 487

heart murmur(s)
causes, 495
classification, 495
late, presystolic, 489
over heart apex, 493
Flint's 488, 493
functional, 461
gradation, 461
Graham Steell, 482
innocent, 461f, 479
aortic systolic, 463
cardiopulmonary extracardiac, 461
classification, 493
continuous, 462
pulmonary systolic, 462f
supraclavicular (carotid), 462, 479
vibration (parasternal), 462
mammary, 462, 466
mesodiastolic, 491
organic, 461f
Still's, 462
systolic, 75, 461f, 486
causes, 494
over base of heart, 477
over heart apex, 469
in second left intercostal space, 479
in second right intercostal space, 474
venous, *see also* venous hum, 464
heart tumours, 760
Hein's test, 539
helminth infestations, 280
hepatic veins, inflammation, 525
thrombosis, 525ff
hepatic vessels, diseases, 520ff
hepatitis, 224, 293, 295ff, 437, 712ff
acute, 497, 535
anicteric, 497
in infectious mononucleosis, 545
infectious, 543
serum, 543, 545
virus, 501, 543, 546, 548, 551, 553
alcoholic, 505
cholestatic, 548f
chronic, 334, 497, 516, 547
active, 498ff, 509
aggressive, 499
benign (persistent), 497f, 501
lupoid, 499, 502
drug-induced, 502, 505, 545
toxic, 545f
hepatolenticular degeneration, 501, 508f
hepatoma, 514ff, 518
in liver cirrhosis, 516
hepatomegaly, 496ff, 503, 506, 509, 514f, 517, 519, 523, 526, 528, 533
and splenomegaly, 510, 523, 527, 532, 545, 562, 575
herpes zoster, 188, 191, 184
hiatal hernia(s), 183
hirsutism, 93
Huddleson's test, 322
hydatid cyst of chest, 631
hydronephrosis, 729
hydrothorax, 634
hyperbilirubinaemia posthepatitic, 498, 540f
hypercalciaemia, 727
hypernephroma, 331
hyperparathyroidism, 725
hyperproteinaemia, 591
hypersplenism, 521, 523
hypertension, arterial, *see* arterial hypertension
portal, *see* portal hypertension
pulmonary, *see* pulmonary hypertension
hypertensive crisis, 493
hypertensive disease, *see also* arterial hypertension, essential, 88, 90f, 610, 710
and atherosclerosis, 103
in elderly, 106
kidney biopsy in, 104
malignant, 91, 94, 113
oedema in, 93
renal function in, 98
nephrotic syndrome in, 104
hyperthermia, 308
hyperventilation, 776
hypoglycaemia, 777
hypokaliaemia, 727
hypotension, orthostatic, 754, 756
iatrogenic, 755
idiopathic, 754
postural, 752
hysteria, 766

ileotyphlitis tuberculous, 276, 362
influenza, 659
interventricular septum, rupture, 438
intestinal distension, 126
iron, 51
absorption, 51f
deficiency, 52
ischaemic heart disease, 81, 86, 384, 406, 412
ECG in, 152
and myocardial infarction, 411

jaundice, 535ff, 543ff, 548f, 553f, 557f
acquired, of infants, 542
causes, 562

jaundice
with conjugated bilirubin, 542ff
constitutional, 552f
extrahepatic, 555ff
familial of newborn, 541
haemolytic, *see* haemolytic jaundice
hepatocellular, 515, 518, 524
hepatogenic, 540, 542f
non-haemolytic, congenital, 540, 542
non-hepatogenic, 536, 542
obstructive, 555
types, 562
with unconjugated bilirubin, 536
Kayser-Fleischer ring, 501, 509
Kerley's lines, 413
kwashiorkor, 44, 286
kyphoskoliosis, cor pulmonale in, 398
lactase activity, deficient, 285, 289
tests for, 287f
lactose intolerance, 286
lambliasis, 280
large intestine, carcinoma, 242f, 252, 273ff
diverticulosis, 243
polyp, 358
stricture, 245
left-ventricular aneurysm, 472, 611
legionellosis, 655
Lermit's sign, 190
leucocytes, active and inactive, 97
leucosarcoma, 297
leucosis, acute, 57
lymphatic, 740
leukaemia, 57f
acute, 528f
hairy cell, 531
lymphoid, 297, 531f, 625
myeloid, 529, 713
leukaemoid reaction, 529, 531
limb arteries, stenosing atherosclerosis, 621
livedo reticularis, 626
liver, abscess, 326, 636
cirrhosis, 134, 136f, 334, 356f, 495, 502ff, 510, 516, 521, 524, 526f, 712
alcoholic, 504
biliary, 505
infectious, 502
Laennec's, 505
micronodular (portal), 508f
cyst(s), 511ff, 519, 558
diseases, as cause of portal hypertension, 134
enlargement, *see* hepatomegaly
fatty infiltration, 499
haemangioma, 519
in heart failure, 496
melanoma, 520
nutmeg, 131
sarcoma, 519
tumours, 331, 513f, 525
benign, 514, 518f
types, 514
Lukin-Libman's sign, 315
lung, abscess, 636
adenoma, 695
atelectasis, 376, 678ff
bird fancier's, 667
carcinoma, 378, 397, 677, 686, 694, 715
caseoma, 696
hydatid disease, 380
infarction, 640, 690f
lymphogranulomatosis, 696
lymphosarcoma, 697
miliary carcinosis, 699
mushroom picker's, 666
occupational diseases, 701
parasitic diseases, 380f
suppuration, 380,
tuberculoma, 696
tuberculosis, *see also* tuberculosis, pulmonary, 379, 636f
lupus erythematosus, systemic, 301, 328f, 640
generalized affection, 293
involvement in diseases, 297
local affection, 293
mediastinal, tumours of, 299ff, 302, 305
tuberculosis, 300, 319
lymphadenopathy, immunoblastic, 295
lymphangiectasis, intestinal, 134, 591, 593, 597
lymph nodes, enlargement, 293ff, 322, 529, 531
causes, 307
lymphogranulomatosis, 282, 293, 298, 300f, 306, 310, 312, 332, 625, 634, 639, 687, 696, 701 705
lymphosarcoma, 282, 295f, 301, 740

macroglobulinaemia, 532
Waldenström's, 625, 723f, 745
malaria, 323
Meckel's diverticulum, 352
mediastinal, cysts, 303, 306
emphysema, 231
organs, compression syndrome, 300
tumour, 302f, 355
megacolon, 328
melaena, 346
mesadenitis, 33f

mesothelioma, 129
pleural, 640
methaemoglobinaemia, congenital, 715
milk sugar tolerance test, 287
mitral heart disease, 404 409
mitral insufficiency, 410, 421, 430, 612
acquired, 470
acute, 435
auscultation signs, 431, 433ff, 469, 491
chronic, 431, 436
congenital, 434, 370
differential diagnosis, aortic stenosis, 488
mitral stenosis, 433
myocardial infarction, 437
tricuspid insufficiency, 429
mixed, 470f
and myocardial infarction, 438
organic, 433, 444
relative, 433, 444
rheumatic, 430, 434
subvalvular, 470f
X-ray in, 432
mitral stenosis, 382, 413, 488f
and aortic insufficiency, 421
aphonic, 429
auscultative signs, 415, 420, 490, 492
cardialgia in, 415
congenital, 489
differential diagnosis, aortic insufficiency, 422
atrial myxoma, 427
atrial septal defect, 426
mitral insufficiency, 433
tricuspid stenosis, 423
ECG, 419f
and mitral insufficiency, 421
rheumatic, 489
thromboembolism in, 414
X-ray, 418, 420
mitral valve, 430, 434
prolapse, 166
mononucleosis infectious, 528, 531, 545
monosaccharide, malabsorption, 285, 288
tolerance test, 288
muscle pain, 184
mushroom intolerance, 289
myelofibrosis, 530
myeloleucosis, chronic, 58
myeloma multiple, 533, 585, 715, 723f, 727, 745
nephrotic syndrome in, 584
myocardial hypertrophy, concentric, 399
myocardial infarction, 81, 85, 147, 149, 188, 194, 217f, 405, 411, 437, 457, 471
arterial pressure in, 196, 223
blood enzyme activity, 164, 207
differential diagnosis, aneurysm of aorta, 221
aortic stenosis, 445
cholecystitis, 21
hepatic colic, 21
pancreatitis, 23
disorders of myocardial contractility, 199
ECG, 165, 200, 206, 214, 218, 412
echocardiography, 210, 216
febrile reaction, 198
gastralgic form, 195
heart sounds in, 195
leucocyte count, 198
pain in, 20ff, 194, 200f, 213, 221
paroxysmal, dyspnoea in, 611f, 615
pulse rate, 196
resorption-necrotic syndrome, 197
rhythm disorders, 195f
scintigraphy, 210
subendocardial, 156
myocardial necrosis, body reaction to, 198
myocarditis, 169, 216, 218, 399, 409, 611
chronic, 172
ECG, 401
idiopathic, 170, 400
pain in, 171, 173
myofibrosis endocardial, 470
myoplegia paroxysmal, 728
myxoedema, 127, 140, 248, 565, 635
myxoma, of left atrium, 489, 492
of right atrium, 395, 426ff, 429

narcolepsy, 765
nephritis, 573, 581, 585, 616
embolic, 574ff
interstitial, 729
lupus, 574ff
nephropathy, analgesic, 729
diabetic, 586
nephrotic syndrome, 138, 569ff, 573, 574ff, 578ff, 583f, 585ff, 634
causes, 572, 604
congenital, 584
drug-induced, 588
nitroglycerin therapy, trial, 159
nycturia, 717

oedema, 564ff, 603
in acute left-ventricular failure, 608
in amyloidosis, 582

oedema
in bacterial endocarditis, 579
causes, 604
in coeliac disease, 597
generalized, 564f
in heart failure, 564, 576
hypoproteinaemic, 565, 571, 581, 599
localized, 564ff
lymphatic, 567
migrating, 402
in nephrotic syndrome, 570
in pregnancy, 568
premenstrual, 568
pulmonary, 608
alveolar, 608
interstitial
oesophagitis, 182
oesophagospasm, 182
oesophagus, carcinoma, 356
diverticulum, 182
varicose veins, bleeding from, 355f, 364
opening snap, 399, 416f
ornithosis, 661
Osler's nodes, 316
osteogenesis imperfecta, 745

pain, 193
panaortitis, murmur, 479
pancreas, carcinoma, 557
pancreatic cholera, 256
differential diagnosis, carcinoid syndrome, 260
gastrinoma, 257
pancreatitis, 140, 558
abdominal pain in, 34f
pancytopenia, familial hypoplastic, 56
paragonimiasis, 381
paranephral abscess, 327
paranephritis, 327
patent ductus arteriosus, *see also* persistent ductus arteriosus, 457, 465f, 468, 776
murmur in, 464f
pellagra, 279
peptic ulcer, 348, 357, 364
differentiation from gastrinoma, 254
periarteritis nodosa, 113, 329, 397, 614
arterial hypertension in, 113
nephrotic syndrome in, 578
pericardial cysts, 306
pericarditis, 213
annular, 408
blood enzyme activity, 215
constrictive, 131, 137f, 408, 587, 610
ECG, 214
echocardiography, 214
with effusion, 389, 402, 410
pain in, 26, 213, 215
pericholangitis, 501
perineum ptosis, 245
periodical disease, 35f, 235, 583
peritoneal pseudomyxoma, 130
peritonitis, 18ff
tuberculous, 128
peritoneum, metastasis of malignant tumours to, 130
persistent ductus arteriosis, *see also* patent ductus arteriosus 484
murmurs in, 485, 489
phaeochromoblastoma, 120, 122
phaeochromocytoma, 120
pleura, empyema, 635, 646
mesothelioma, 640
pleural pain, 181
pleural shock, 759
pleurisy, 629ff
dry, 232
with effusion, 629
causes, 632, 641
differential diagnosis, 630, 642
eosinophilic, 641
identification, 629
non-suppurated, 637
purulent, 636
lupoid, 640
pneumonia, 18, 382, 636, 643ff
abdominal pain in, 18f
acinetobacterial, 655
acute, 643ff
adenovirus, 658, 697
allergic, 665ff
anaerobic, 650
aspiration, 376, 671
bacterial, Gram-negative, 651ff, 663
Gram-positive, 644ff, 663f, 674ff, 680, 684, 688f
chlamydian, 661
Coli, 653, 689
diffuse miliary, 697
enterobacterial, 654
Haemophilus influenzae, 651
hydrocarbon, 670
influenza, 659, 663, 681
interstitial, 398, 667
Klebsiella, 652, 681, 697
in legionellosis, 655
lipoid, 669
lobar, 226, 680
lobular, 630, 661, 681, 688
mycoplasmal, 567
ornithosis, 661, 664
pneumococcal, 635, 644ff, 674
prehilar, 702

pneumonia
Proteus, 654, 689
pyocyaneus, 653
in Q fever, 662, 664
rickettsial, 661
segmental, 680
Serratia, 654
staphylococcal, 647f, 674, 697
streptococcal, 659f, 697
unresolved, 674ff
virus, 656, 663, 680, 689
pneumothorax, 230
spontaneous, 607, 633
pollakiuria, 717
polycystic kidney disease, 100f, 512
polycythaemia, 525, 625, 708ff
causes, 716
congenital, 713f
hypoxic, 714
relative, 716
secondary, 713f
types, 716
vera, 708f
polydipsia, 720, 725
causes, 732
involuntary, 720, 730f
polyuria, 717f, 725ff
causes, 717, 732
in diabetes insipidus, 720
in diabetes mellitus, 718
in hyperparathyroidism, 726
in thyrotoxicosis, 728
porphyria, acute, 31, 248
portal cirrhosis, 124, 135
portal hypertension, 124, 131, 133, 136f, 355, 364, 503, 515, 517, 521f, 527
extrahepatic, 357
idiopathic, 523
intrahepatic, 356
primary, 523
secondary, 524
portal vein, stenosis, 132, 135, 523
thrombosis, 135, 520ff, 524f
preinfarction state, 147
protein, deficiency in diet, 43
loss through gastro-intestinal tract, 44, 571, 600, 603
assessment, 593
pseudopolycythaemia, 716
pseudoxanthoma elasticum, 353
pulmonary arteriovenous, aneurysm, 467
pulmonary artery, amyloid deposits, 397
dilatation, 386, 418, 486
embolism, 226
stenosis, 444, 468, 610
thromboembolism, 350, 614
pulmonary emphysema, 397
obstructive, paroxysmal dyspnoea in, 607
pulmonary haemorrhage, 375f
causes, 383
pulmonary heart disease, *see* cor pulmonale
pulmonary hypertension, 138, 414, 418, 473, 486
and loss of consciousness, 774ff
primary, 396
pulmonary insufficiency, 489
congenital, 384
relative, 385
pulmonary oedema, 608, 610, 613, 616
in acute left-ventricular failure, 608
pulmonary sclerosis, interstitial, 398
pulmonary stenosis, 386, 393, 477, 479, 714
heart sounds, 479
infundibular, 387, 480
murmur, 479
subinfundibular, 386
supravalvular, 387, 481
pulmonary thromboembolism, 690
purgatives, abuse, 247, 252
purpura, 734ff
causes, 747f
in congenital connective-tissue diseases, 744
drug-induced, 739, 747
in haemorrhagic vasculitis, 741
in infectious diseases 744
non-thrombocytopenic, 741f
Schoenlein-Henoch, anaphylactoid, 741
in scurvy, 743
thrombocytopenic, *see also* disease, Werlhof's, 134, 364, 736ff
pyaemia, 313
pyelonephritis, 95, 98f, 105, 127, 327, 587, 729
arterial hypertension in, 95ff, 101
provocative tests, 97
pyelophlebitis, 522ff

rectal mucosa, prolapse, 245
rectum, achalasia, 239
red-cell membrane anomaly, 59
renin hypersecretion, 118
renal artery, atherosclerosis, 107
renal veins, thrombosis, 573
rheumatic heart disease, 81, 317f, 395
rheumatoid arthritis, 328, 581, 624, 640, 745
rigor, 311

sarcoidosis, 298, 300, 700
Schilling's test, 50
Schmorl's body, 189
scleroderma, 249, 576, 624, 740
sepsis, 312f
  meningococcal, 323
  pulmonary oedema in, 617
septicaemia, 313
  blood culture in, 314
sinus automaticity disorders, 73
small intestine, haematosarcoma, 283
  lymphosarcoma, diffuse, 599
    differentiation from Whipple's disease, 603
  tumours, 598
spherocytosis congenital, 59f
splenomegaly, 504, 507, 509f, 515, 520f, 523f, 526ff, 529f, 533, 536, 538
sprue, 594
Spurling's sign, 190
stenocardia, *see* angina pectoris
Sternheimer-Mulbin cells, 97f
stomach, diverticulum, 351
stomatocytosis congenital, 60
string sign, 244, 292
strongyloidiasis, 381
struma, ovarian, 370
subaortic stenosis, hypertrophic, 399, 418, 446
  muscular type, 472
subdiaphragmatic abscess, 183, 324, 637
subhepatic abscess, 325
syncope, *see also* consciousness loss, transient, 756, 779,
  vasodepressor, 751, 781
syndrome, abnormal rectal dilatation, 240
  Adams-Stokes-Morgagni, 770, 772
  afferent loop, 48
  anterior chest wall, 185
  aortic arch, 770f
  Banti's, 523
  Budd Chiari, 525
  carcinoid, 257, 259f
  carotid sinus, 768ff
  cervical rib, 622
  Conn's, 114f, 727f
  Crigler-Najjar 541
  defibrination, 740
  diencephalic, 121, 126
  Dubin-Johnson, 552f, 555
  Ehlers-Danlos, 227, 744f
  E senmenger's, 484
  Fanconi's, 723
  Gilbert's 499, 540
  Groesbeck-Imerslund, 45, 48
  hyperkinetic, 487
  Itsenko-Cushing's, 117
  Kimmelstiel-Wilson's, 101
  Loeffler's, 668
  Lucey-Driscoll, 542
  Mackle-Well, 583
  malabsorption, 45, 50, 282, 287, 290, 565, 601
  Mallory-Weiss, 349, 353
  manubrio-sternal, 190f
  Marchiafava-Micheli, *see* haemoglobinuria, nocturnal
  Marfan's, 179, 227, 453, 470
  Meig's, 140, 634
  Meniére's, 765
  Mikulicz's, 531
  milk-alkali, 726
  nephrotic, *see* nephrotic syndrome
  Plummer-Vinson's, 52
  post-hepatitic, 498
  postinfarction, 215
  premenstrual, 568f
  Raynaud's, 93, 187, 532, 619ff
    causes, 627
    occupational, 620
  Rotor's 552f, 555
  scalenus (anticus), 186, 623
  sick sinus, 84
  Shereshevsky-Turner, 118
  shoulder-hand, 187f
  Shy-Drager, 754
  slipping costal cartilage, 184
  Tietze's, 191
  vertebral artery insufficiency, 190
  Waterhouse-Friderichsen, 323
  Wolff-Parkinson-White, 83, 154, 779
  xiphodynia, 192
syphilis, enlargement of lymph nodes in, 302
systemic lupus erythematosus, 500, 623, 640, 740, 745
  nephrotic syndrome in, 574, 578
systolic, click, 168
  gallop, 166

tachyarrhythmia, 613
tachycardia, atrial, 77, 79, 83
  atrioventricular, 78
  ECG in, 77f
  sinus, 73
  supraventricular, 76, 83, 613
  ventricular, 773
telangiectases, 377
  congenital 252, 744
teratoma(s), mediastinal, 303
thalassaemia, 53, 57, 63, 510, 538
thromboangiitis obliterans, 621

thrombocytopenia, 736
causes, 747
thrombopathy, 745
thrombophlebitis, 334
thymoma, 305
thymus, tumours, 305
thyroid, 367
adenoma toxic, 368
functional tests, 369
tumours, 369, 373
thyroiditis, 372
thyrotoxicosis, 367, 473
in diffuse toxic goitre, 367
due to iodine, 371
due to thyroid preparations, 372
in malignant tumours, 371
monosymptomatic, 334
in ovarian struma, 370
in thyroid-stimulating hormone secretion, 371
tracheitis, acute, and chest pain, 180
trichomoniasis intestinal, 280
tricuspid insufficiency, 423f, 472, 482
murmur, 420, 470, 473
organic, 425
relative, 425
tricuspid stenosis, 389, 423, 491
trihalose, reduced activity, 289
tuberculoma, 696
tuberculosis, 319f
fever in, 319
haematogenic-disseminated, 698
pulmonary, *see also* lung, tuberculosis, 226, 378, 676ff, 681, 692f, 703
of small intestine, 284
tumour(s), fever in, 330
heart failure in, 391
of kidneys, 330
mediastinal, 306, 355
neurogenic, 302f

ulcerative colitis, 127, 265ff, 359, 362
abdominal pain in, 265
diarrhoea in, 265, 275
differential diagnosis, amoebiasis, 269f
bacillary dysentery, 268
balantidiasis, 270
carcinoma of large intestine, 276
functional diarrhoea, 291
granulomatous colitis, 272
forms, 266
intestinal haemorrhage in, 265f, 272
proctosigmoidoscopy, 266
urolithiasis and arterial hypertension, 100

Valsalva's sinus aneurysm, 227ff, 453, 455, 466
differentiation from patent ductus arteriosus, 457
heart failure in, 456
rupture, 456f, 466
valvular disease, rheumatic, 389
vasculitis haemorrhagic, 36f, 363, 576, 741f
of drug origin, 743
nephrotic syndrome in, 577f
vasospasm peripheral, 619ff
causes, 627
vegetative crises, 162, 186
vena cava thrombosis, 132, 526
venous hum, 464f
abdominal, 468
cervical, 465, 468
ventricular septal defect, 444, 453, 483, 776
murmur, 469, 483, 489
Vidal's test, 321
vitamin B_{12}, absorption, 45
deficiency, 45ff
anaemia in, 45, 50, 57
causes, 89
signs, 47

Wilm's tumour, 119
Wright's test, 322

Printed in the Union of Soviet Socialist Republics